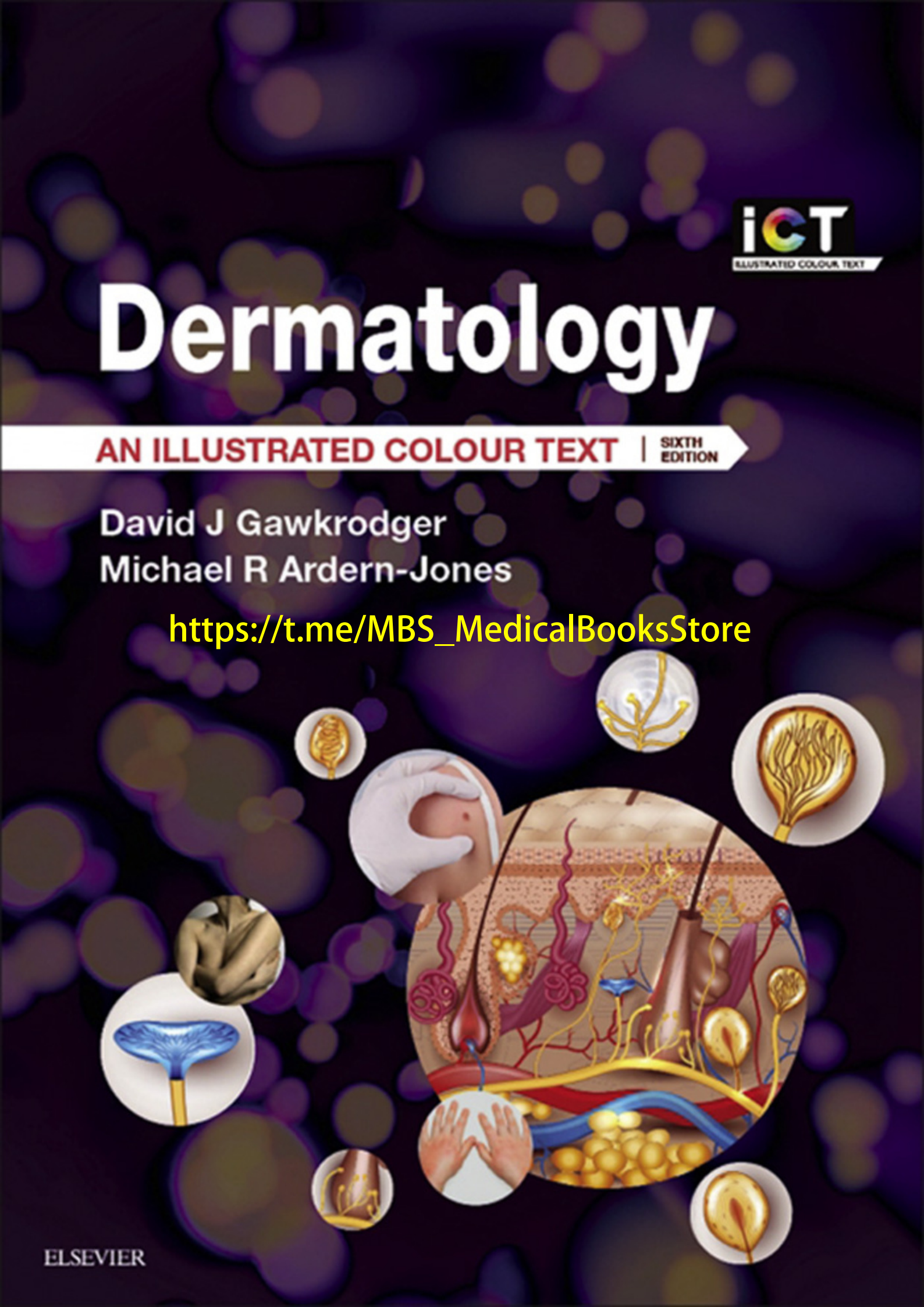
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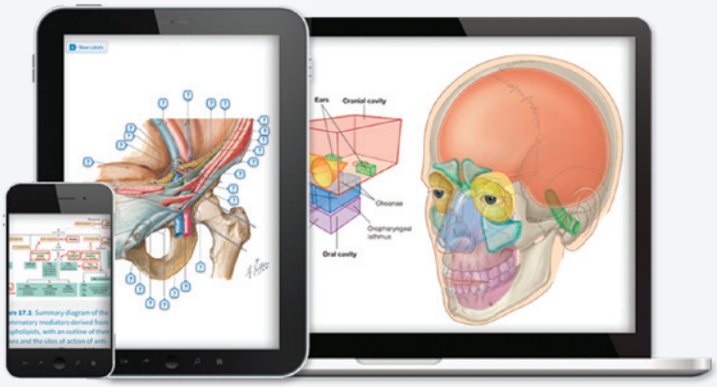

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Dermatology

AN ILLUSTRATED COLOUR TEXT

Sixth Edition

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Dermatology

AN ILLUSTRATED COLOUR TEXT

Sixth Edition

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Preface to the sixth edition

There has been a near revolution in how a published medical text is handled by its users since we wrote the fifth edition of this work in 2011. For this type of book, there will be considerable usage online. The content and presentation of the sixth edition of this book has been developed to accommodate readers' likely use in the smartphone age. Our publishers, Elsevier, have been of considerable assistance in this task, providing the platform for the delivery of an interactive, searchable and well illustrated text.

In order to make use of the opportunities offered by online publication, we have increased the flexibility of the educational level of the text. Previously we aimed to write and illustrate a book that was suitable for medical students and general practitioners but which would also appeal to the early trainee in dermatology. This is still the case, and the printed version has been fully updated, but online publication has given us the chance to broaden the scope of the book. We have added some material at a higher level that can be accessed by those that opt to use it, whilst bolstering the basic strengths of the text through the use of additional illustrations.

Online publishing has allowed us, for each topic covered, to introduce innovations. These include self-assessment questions, flashcards, a picture gallery of dermatological diseases and direct Internet links to other sources of information and reference. It has also been possible to highlight throughout the text, new treatments and dermatological emergencies.

We are aware that the specialty of dermatology is constantly changing. There is presently a greater emphasis than ever before on skin cancer, its recognition and management, and we have reflected this in our content. Other areas that have developed into subspecialisms, which have required additional text, include genital dermatoses, psychodermatology, cosmetic procedures, and advances in dermatologic surgery.

We trust that our target audience of medical students, family doctors, hospital residents, specialty registrars in dermatology or internal medicine, and specialist nurses will continue to find our book helpful in the diagnosis and management of patients with skin diseases.

David J. Gawkrodger and
Michael R. Ardern-Jones
Sheffield and Southampton, 2015

Preface to the first edition

Recent advances in publishing technology and book presentation demand that a modern text be attractively and concisely presented, in colour and at an affordable price. This is essential for success in a very competitive market. In writing this book, I have attempted to present an introductory dermatology text for the 1990s, using a format of individually designed double-page spreads, generously illustrated with colour photographs, line drawings, tables, bulleted items and 'key point' summaries. This unique approach, which deals with each topic as an educational unit, allows the reader better accessibility to the facts and greater ease in revision than is possible with a conventional textbook.

The book is aimed at medical students but contains sufficient detail to be of use to family practitioners, physicians in internal medicine, registrars or residents in dermatology and dermatological nurses. The contents are divided into three sections. The first presents a scientific basis for the understanding of and clinical approach to skin disease. The second details the major dermatological conditions, and the third outlines special topics, such as photoageing and dermatological surgery, that are of current importance or that are poorly dealt with in other textbooks.

David J. Gawkrodger
Sheffield 1992

Acknowledgements

In the production of the sixth edition of this book it is a pleasure to acknowledge the contribution of the publishing staff at Elsevier, notably Jeremy Bowes, Alisa Laing and Kim Benson. We are grateful to colleagues who have advised on various aspects of the book, especially to Dr Louise Ardern-Jones for her detailed review.

We thank colleagues who have generously provided figures for this and previous editions, including Dr E.C. Benton of Edinburgh, Dr J.E. Bothwell of Doncaster, Dr J.S.C. English of Nottingham, Dr J. Bowling of Oxford (dermoscopy images), the late Dr S.M. Morley of Dundee, Dr M. Shah of Burnley, Dr H.S. Ghura of Salford, and Dr A.J.G. McDonagh, Dr A.G. Messenger, Dr C. Yeoman, Mr D. Dobbs, Professor S.S. Bleehen and Dr C.I. Harrington of Sheffield, and also Dr Efrem Eren, for provision of autoantibody fluorescence images.

We are grateful to the following for advice or for the provision of illustrations: Professor R.StC. Barnetson, Dr G.W. Beveridge, Professor Chris Bunker (University College Hospital, London), Dr P.K. Buxton, Dr G.B. Colver, the late Professor F.J.G. Ebling, Dr M.E. Kesseler, Dr Fiona Lewis (St Thomas Hospital, London), Dr C. McGibbon, Dr A. McMillan, Mrs E. McVittie, Dr C.StJ. O'Doherty, Dr Glenda Sobey (Sheffield Children's Hospital), Miss M.J. Spencer, Dr M.D. Talbot and the late Dr A.E. Walker.

We also thank those patients who gave permission for their faces to be shown without eyebars.

Contents

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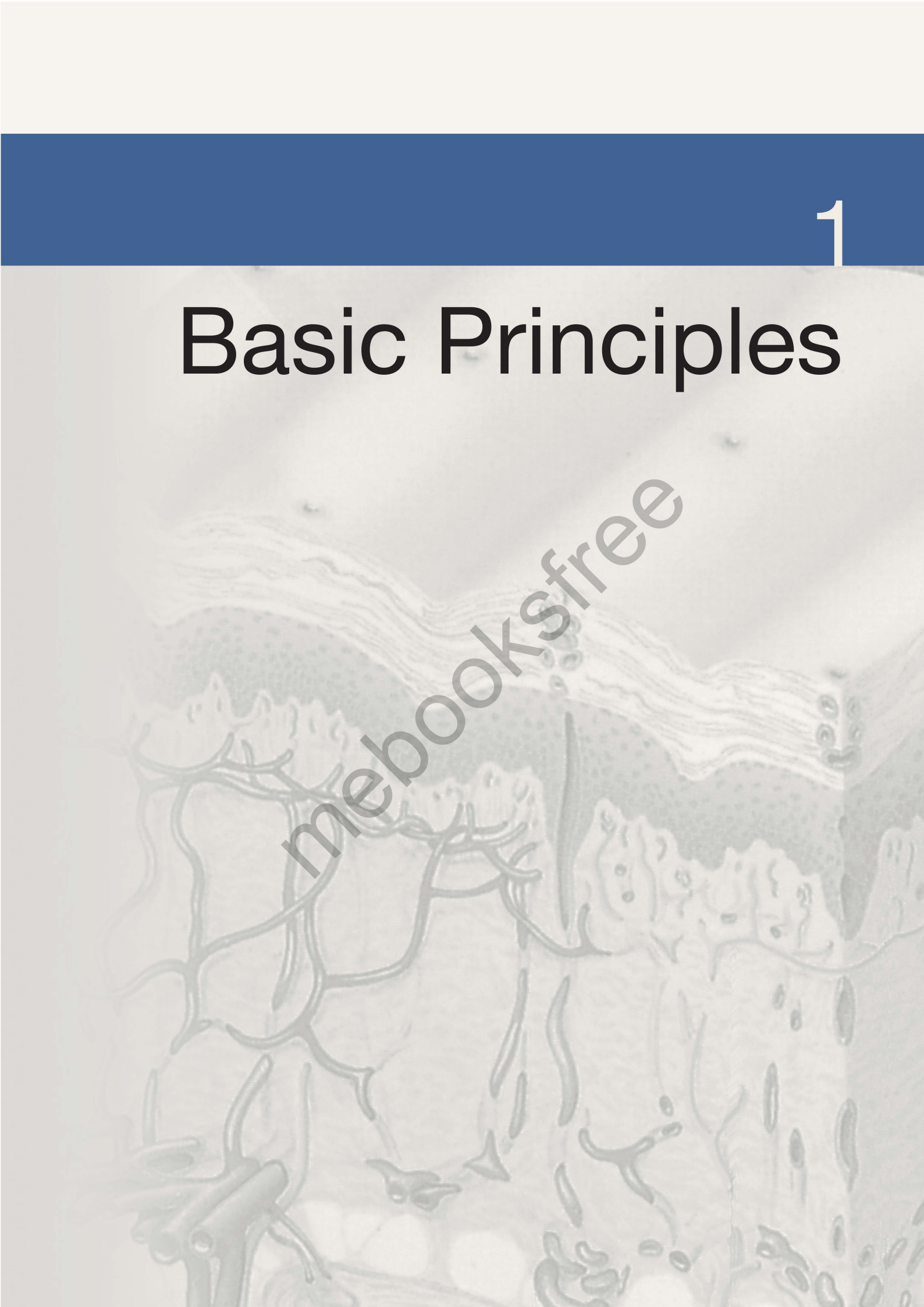
1

Basic Principles



1 Microanatomy of the skin

The skin is one of the largest organs in the body, having a surface area of 1.8 m^2 and making up about 16% of body weight. It has many functions, the most important of which is as a barrier to protect the body from noxious external factors and to keep the internal systems intact.

Skin is composed of three layers: the epidermis, the dermis and the subcutis (Fig. 1.1), and supports a complex population of microflora on the surface (skin microflora) (p. 10).

Epidermis

The epidermis is a stratified squamous epithelium that is about 0.1 mm thick, although the thickness is greater (0.8–1.4 mm) on the palms and soles. Its prime function is to act as a protective barrier. The main cells of the epidermis are *keratinocytes*, which produce the protein keratin. Keratinocytes are squamous cells functionally similar to all other structural epithelial cells as found in the airways and gastrointestinal tract. Keratinocytes differentiate upwards through the epidermis and their maturation states (p. 6) are divided into four stages (layers) (Fig. 1.2a).

Basal cell layer (stratum basale)

The basal cell layer of the epidermis is composed mostly of keratinocytes, of which a small proportion are stem cells and continuously divide. The cells contain keratin tonofilaments (p. 6) and are secured to the basement membrane (Fig. 1.2b) by hemidesmosomes. *Melanocytes* make up 5–10% of the basal cell population. These cells synthesize melanin (p. 7) and transfer it in melanosomes via dendritic processes to neighbouring keratinocytes.

Melanocytes are most numerous on the face and other exposed sites, and are of neural crest origin. *Merkel cells* are also found, albeit infrequently, in the basal cell layer. These cells are closely associated with terminal filaments of cutaneous nerves and seem to have a role in sensation. Their cytoplasm contains neuropeptide granules, as well as neurofilaments and keratin. Basal keratinocytes synthesise antimicrobial peptides, important in defence against bacteria.

Prickle cell layer (stratum spinosum)

Daughter basal cells migrate upwards to form this layer of polyhedral cells, which are interconnected by desmosomes (the 'prickles' seen at light microscope level). Keratin tonofibrils form a supportive mesh in the cytoplasm of these cells. *Langerhans cells* are mostly found in this layer; these dendritic, immunologically active cells are described fully on page 10.

Granular cell layer (stratum granulosum)

Cells become flattened and lose their nuclei in the granular cell layer. Keratohyalin granules are seen in the cytoplasm together with membrane-coating granules (which expel their lipid contents into the intercellular spaces).

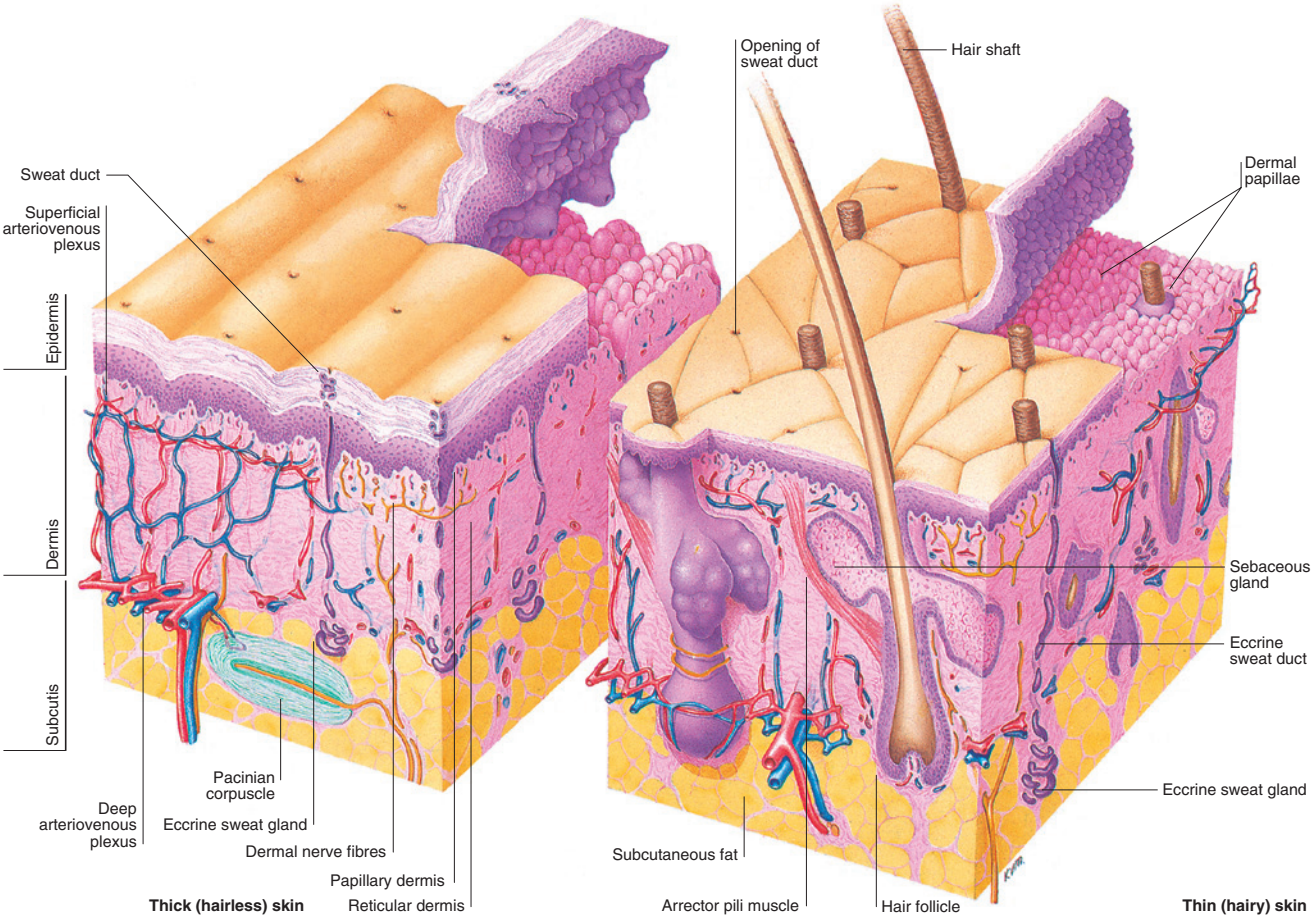


Fig. 1.1 Structure of the skin. The diagram shows a comparison between thick, hairless skin (plantar and planar) and thinner, hirsute skin.

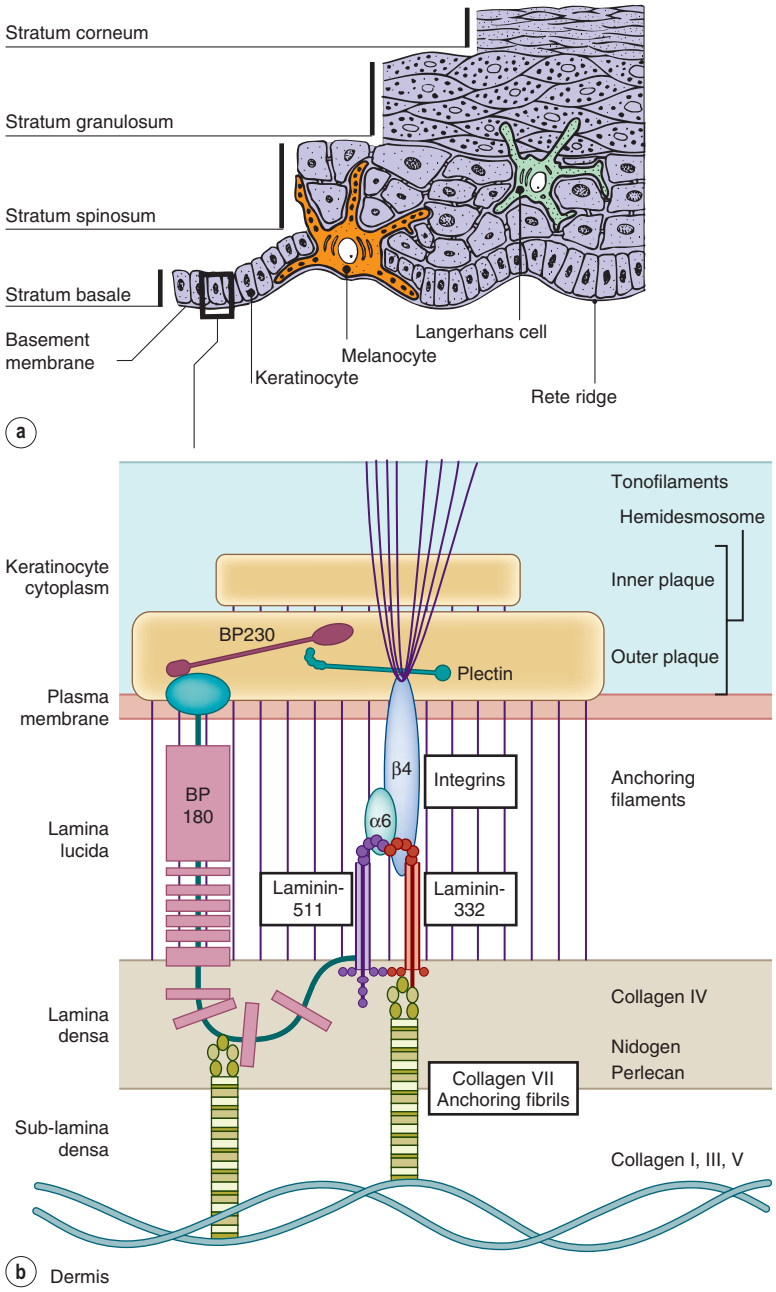


Fig. 1.2 Cross-sectional anatomy of the epidermis. (a) Layers of the epidermis and other structures. (b) Detailed view of the basement membrane zone at the dermoepidermal junction. Components are arranged in three layers. The lamina lucida is traversed by filaments connecting the basal cells with the lamina densa, from which anchoring fibrils extend into the papillary dermis. These laminae are the sites of cleavage in certain bullous disorders (Table e1.1). For illustrative purposes only α6β4 integrins are shown, but others such as α3β1, α6β1 are also important.

Box 1.1 Embryology of the skin

The epidermis (ectoderm) begins to develop at 4 weeks of life, and, by 7 weeks, flat cells overlying the basal layer form the periderm (which is eventually castoff). Nails start to take shape at 10 weeks. The dermis (mesoderm) develops at 11 weeks, and, by 12 weeks, indented basal buds of the epidermis form the hair bulbs, with dermal papillae supplying vessels and nerves. Fingerprint ridges are determined by 17 weeks' gestation. Maturation of the epidermis into a fully functional protective barrier continues throughout gestation and, because of this, pre-term infants are now frequently cared for with plastic occlusion to replicate this function.

Horny layer (stratum corneum)

The end result of keratinocyte maturation can be found in the horny layer, which is composed of sheets of overlapping non-viable polyhedral cornified cells with no nuclei (corneocytes). The layer is several cells thick on the palms and soles, but less thick elsewhere. The corneocyte cell envelope is broadened, and the cytoplasm is replaced by keratin tonofibrils in a matrix formed from the keratohyalin granules. Cells are stuck together by lipid glue that is partly derived from membrane-coating granules.

Dermis

The dermis is defined as a tough supportive connective tissue matrix, containing specialized structures, found immediately below and intimately connected with the epidermis. It varies in thickness, being thin (0.6 mm) on the eyelids and thicker (≥3 mm) on the back, palms and soles. The *papillary dermis* – the thin upper layer of the dermis – lies below and interdigitates with the epidermal rete ridges. It is composed of loosely interwoven collagen. Coarser and horizontally running bundles of collagen are found in the deeper and thicker *reticular dermis.*

Collagen fibres make up 70% of the dermis and impart a toughness and strength to the structure. *Elastin* fibres are loosely arranged in all directions in the dermis and provide elasticity to the skin. They are numerous near hair follicles and sweat glands, and less so in the papillary dermis. The *ground substance* of the dermis is a semisolid matrix of glycosaminoglycans (GAGs), which allows dermal structures some movement (p. 8).

The dermis contains fibroblasts (which synthesize collagen, elastin, other connective tissue and GAGs), dermal dendritic cells, mast cells, macrophages and lymphocytes.

Subcutaneous layer

The subcutis consists of loose connective tissue and fat (commonly 1–3 cm thick on the abdomen).

Microanatomy

- The skin constitutes 16% of body weight, with a surface area of 1.8 m^2.
- Structure and thickness vary with site.
- The epidermis is the outer covering, mainly composed of keratinocytes arranged in four layers, namely stratum corneum, stratum granulosum, stratum spinosum and stratum basale.
- The epidermis also contains melanocytes and Langerhans cells.
- The thickness of the epidermis varies from 0.1 mm to 0.8–1.4 mm on the palms and soles.
- The dermis is supportive connective tissue, mainly collagen, elastin and glycosaminoglycans. The thickness varies between 0.6 mm (e.g. eyelids) and 3 mm (e.g. back and soles).
- The dermis contains fibroblasts that synthesize the collagen, elastic fibres and glycosaminoglycans. Dermal dendritic cells are also found together with other immunocompetent cells.

Table e1.1 **Diseases associated with genetic deficiency or antibody targeting of ultrastructural components**

Target protein	Disease associated with gene mutation	Disease associated with autoimmune antibody
Desmoplakin	Lethal acantholytic epidermolysis bullosa simplex	
Keratin 5/14	Epidermolysis bullosa simplex	
Plakophilin-1	Epidermolysis bullosa simplex (suprabasal)	
Plectin	Epidermolysis bullosa simplex Ogna/with muscular dystrophy	
BP180		Bullous pemphigoid, mucous membrane pemphigoid, pemphigoid gestationis, linear IgA disease
BP200		Bullous pemphigoid
BP230		Bullous pemphigoid, mucous membrane pemphigoid, pemphigoid gestationis, linear IgA disease
α6β4 integrin	Epidermolysis bullosa simplex with pyloric atresia Junctional epidermolysis bullosa with pyloric atresia	Mucous membrane pemphigoid
Laminin 332	Junctional epidermolysis bullosa	Mucous membrane pemphigoid
Collagen VII	Dominant dystrophic epidermolysis bullosa	Mucous membrane pemphigoid, linear IgA disease, epidermolysis bullosa acquisita, bullous SLE
LAD285		Linear IgA disease

Further reading – online sources

Further information on the skin anatomy, histology and ultrastructural architecture can be accessed via: http://www.msdmanuals.com/en-gb/professional

2 Derivatives of the skin

Hair

Hairs are found over the entire surface of the skin, with the exception of the glabrous skin of the palms, soles, glans penis and vulval introitus. The density of follicles is greatest on the face. Embryologically, the hair follicle has an input from the epidermis, which is responsible for the matrix cells and the hair shaft, and the dermis, which contributes to the papilla, with its blood vessels and nerves.

There are three types of hair:

1. *Lanugo* hairs are fine and long, and are formed in the fetus at 20 weeks' gestation. They are normally shed before birth, but may be seen in premature babies.
2. *Vellus* hairs are the short, fine, light-coloured hairs that cover most body surfaces.
3. *Terminal* hairs are longer, thicker and darker, and are found on the scalp, eyebrows, eyelashes and also on the pubic, axillary and beard areas. They originate as vellus hair; differentiation is stimulated at puberty by androgens.

Structure

The hair follicle is an invagination of the epidermis containing a hair. The portion above the site of entry of the sebaceous duct is the infundibulum. The hair shaft consists of an *outer cuticle* that encloses a cortex of packed keratinocytes with (in terminal hairs) an *inner medulla* (Fig. 2.1). The germinative cells are in the hair bulb; associated with these cells are melanocytes, which synthesize pigment. The *arrector pili* muscle is vestigial in humans; it contracts with cold, fear and emotion to erect the hair, producing 'goose pimples'.

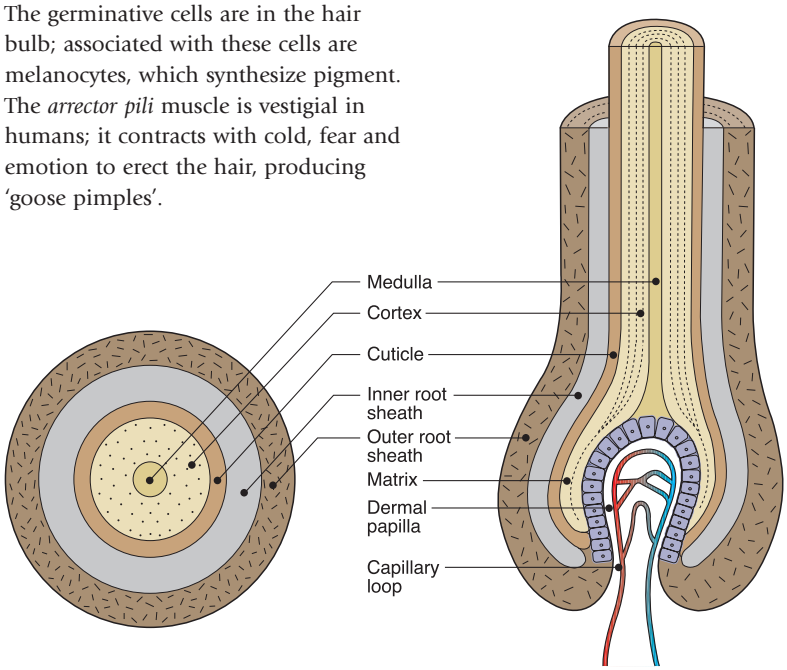


Fig. 2.1 Structure of the hair follicle.

Nails

The nail is a phylogenetic remnant of the mammalian claw and consists of a plate of hardened and densely packed keratin. It protects the fingertip and facilitates grasping and tactile sensitivity in the finger pulp.

Structure

The *nail matrix* contains dividing cells which mature, keratinize and move forward to form the *nail plate* (Fig. 2.2). The nail plate has a thickness of 0.3–0.5 mm and grows at a rate of 0.1 mm/24 h for the fingernail. Toenails grow more slowly. The *nail bed*, which produces small amounts of keratin, is adherent to the nail plate. The adjacent dermal capillaries produce the pink colour of the nail; the white lunula is the visible distal part of the matrix. The *hyponychium* is the thickened epidermis that underlies the free margin of the nail.

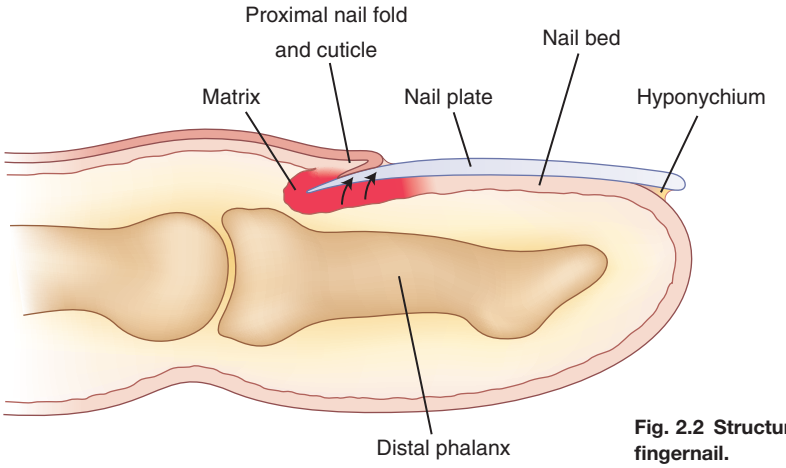


Fig. 2.2 Structure of the fingernail.

Sebaceous glands

Sebaceous glands are found associated with hair follicles (Fig. 2.3), especially those of the scalp, face, chest and back, and are not found on non-hairy skin. They are

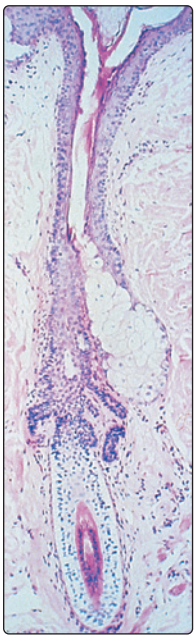


Fig. 2.3 Sebaceous gland in association with a hair follicle. The gland becomes active at puberty.

(see Hair growth in Ch. 3; and Ch. 35 – Disorders of hair).
(see Ch. 36 – Disorders of nails).
(see Acne in Ch. 34).

formed from epidermis-derived cells and produce an oily sebum, the function of which is uncertain. The glands are small in the child, but become large and active at puberty, being sensitive to androgens. Sebum is produced by holocrine secretion, in which the cells disintegrate to release their lipid cytoplasm.

Sweat glands

Sweat glands (Fig. 2.4) are tube-like and coiled glands, located within the dermis, which produce a watery secretion. There are two separate types: eccrine and apocrine.

Eccrine

Eccrine sweat glands develop from downbudding of the epidermis. The secretory portion is a coiled structure in the deep reticular dermis; the excretory duct spirals upwards to open onto the skin surface. An estimated 2.5 million sweat ducts are present on the skin surface. They are universally distributed, but are most profuse on the palms, soles, axillae and forehead where the glands are under both psychological and thermal control (those elsewhere being under thermal control only). Eccrine sweat glands are innervated by sympathetic (cholinergic) nerve fibres.

Apocrine

Also derived from the epidermis, apocrine sweat glands open into hair follicles and are larger than eccrine glands. They are most numerous around the axillae, perineum and areolae. Their sweat is generated by 'decapitation' secretion of the gland's cells and is odourless when produced; an odour develops after skin bacteria have acted upon it. Sweating is controlled by sympathetic (adrenergic) innervation. The apocrine glands represent a phylogenetic remnant of the mammalian sexual scent gland.

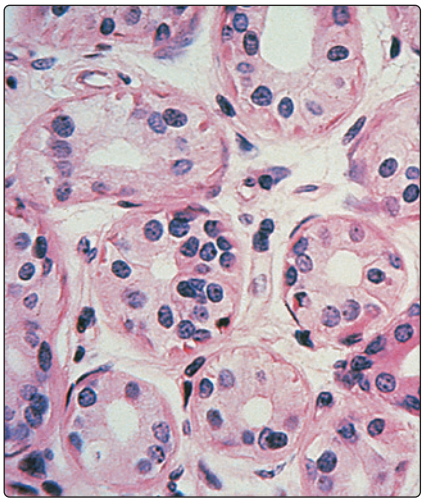


Fig. 2.4 Sweat gland. A cross-section through the coiled secretory portion of an eccrine sweat gland, situated deep in the dermis.

Other structures in skin

Nerve supply

The skin is richly innervated (Fig. 2.5), with the highest density of nerves being found in areas such as the hands, face and genitalia. All nerves supplying the skin have their cell bodies in the dorsal root ganglia. Both myelinated and non-myelinated fibres are found. The nerves contain neuropeptides, e.g. substance P.

Free sensory nerve endings are seen in the dermis and also encroaching into the epidermis where they may abut onto *Merkel cells*. These nerve endings detect pain, itch and temperature. Specialized corpuscular receptors are distributed in the dermis, such as the *Pacinian corpuscle* (detecting pressure and vibration) and touch-sensitive *Meissner's corpuscles*, which are mainly seen in the dermal papillae of the feet and hands.

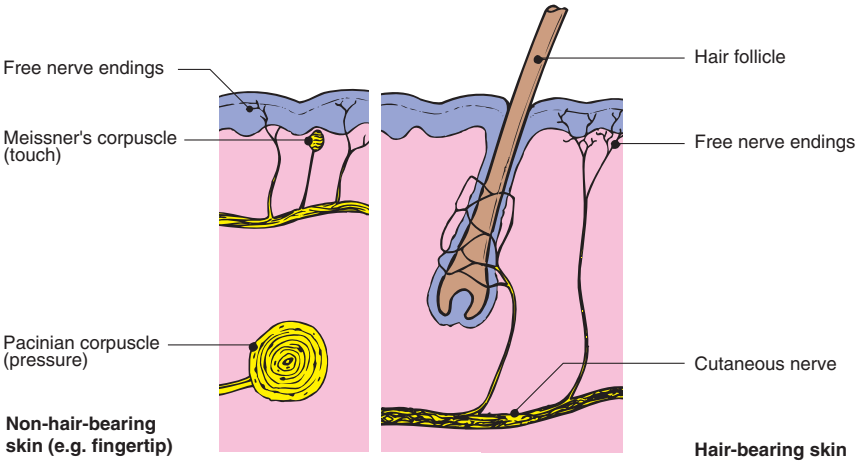


Fig. 2.5 Nerve supply to the skin.

Autonomic nerves supply the blood vessels, sweat glands and arrector pili muscles. The nerve supply is dermatomal with some overlap.

Blood and lymphatic vessels

The skin also has a rich and adaptive blood supply. Arteries in the subcutis branch upwards, forming a superficial plexus at the papillary/reticular dermal boundary. Branches extend to the dermal papillae (Fig. 2.6), each of which has a single loop of capillary vessels, one arterial and one venous. Veins drain from the venous side of this loop to form the mid-dermal and subcutaneous venous networks. In the reticular and papillary dermis, there are arteriovenous anastomoses that are well innervated and concerned with thermoregulation (p. 7).

The lymphatic drainage of the skin is important, and abundant meshes of lymphatics originate in the papillae and assemble into larger vessels that ultimately drain into the regional lymph nodes.

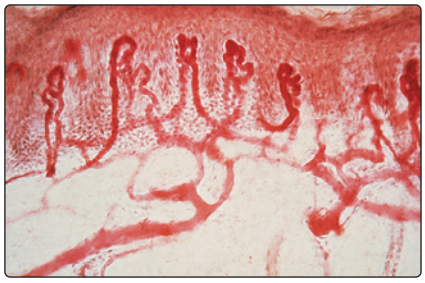


Fig. 2.6 Superficial dermal blood vessels. Capillary loops branch off the superficial vascular plexus and extend into each dermal papilla.

Derivatives

- Sebaceous glands, associated with hair follicles, are androgen sensitive.
- Vellus hairs cover most body surfaces; terminal hairs occur on the scalp, beard, axillary and pubic areas.
- Skin has extensive nerve networks with specialized nerve endings.
- Skin has a rich and adaptive blood supply; lymphatics drain to regional lymph nodes.
- Eccrine sweat glands, with sympathetic innervation, are under thermal/psychological control; apocrine glands are largely vestigial in humans.

(see Hyperhidrosis in Ch. 34).

Further reading

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3 Physiology of the skin

The skin is a metabolically active organ with vital functions (Box 3.1), including the protection and homeostasis of the body.

Box 3.1 Functions of skin

- Presents barrier to physical agents
- Protects against mechanical injury
- Antimicrobial peptides have a bactericidal effect
- Prevents loss of body fluids
- Reduces penetration of UV radiation
- Helps to regulate body temperature
- Acts as a sensory organ
- Affords a surface for grip
- Plays a role in vitamin D production
- Acts as an outpost for immune surveillance
- Communication – cosmetic appearance

Keratinocyte maturation

The differentiation of basal cells into dead, but functionally important, corneocytes is a unique feature of the skin. The horny layer is important in preventing all manner of agents from entering the skin, including micro-organisms, water and particulate matter. Antimicrobial peptides of the defensin and cathelicidin classes, present on the epidermal surface, have anti-bacterial and anti-viral activity. The epidermis also prevents the body's fluids from getting out.

Epidermal cells undergo the following sequence during keratinocyte maturation (Fig. 3.1):

1. Stem cells in the *basal layer* divide (continuously) into one new stem cell and a transit amplifying cell. Transit amplifying cells proliferate briefly and then progress upwards and undergo terminal differentiation.
2. In the *prickle cell layer*, cells change from being columnar to polygonal. Differentiating keratinocytes synthesize keratins, which aggregate to form tonofilaments. The *desmosomes* connecting keratinocytes are composed of the structural molecules cadherins, desmogleins and desmocollins. Desmosomes distribute structural stresses throughout the epidermis and maintain a distance of 20 nm between adjacent cells.
3. In the *granular layer*, enzymes induce degradation of nuclei and organelles. Keratohyalin granules containing filaggrin provide an amorphous protein matrix for the tonofilaments. Membrane-coating granules attach to the cell membrane and release an impervious lipid-containing cement, which contributes to cell adhesion and to the *horny layer* barrier.
4. In the *horny layer*, the dead, flattened corneocytes have developed thickened cornified envelopes containing involucrin that encase a matrix of keratin macrofibres aligned by filaggrin. The strong disulphide bonds of the keratin provide strength to the stratum corneum, but the layer is also flexible and can absorb up to three times its own weight in water. However, if it dries out (i.e. water content falls below 10%), pliability fails.
5. The corneocytes are eventually shed from the skin surface after degradation of the lamellated lipid and loss of desmosomal intercellular connections.

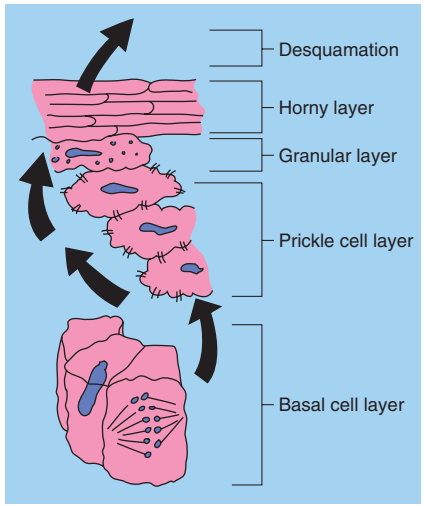


Fig. 3.1 Keratinocyte maturation.

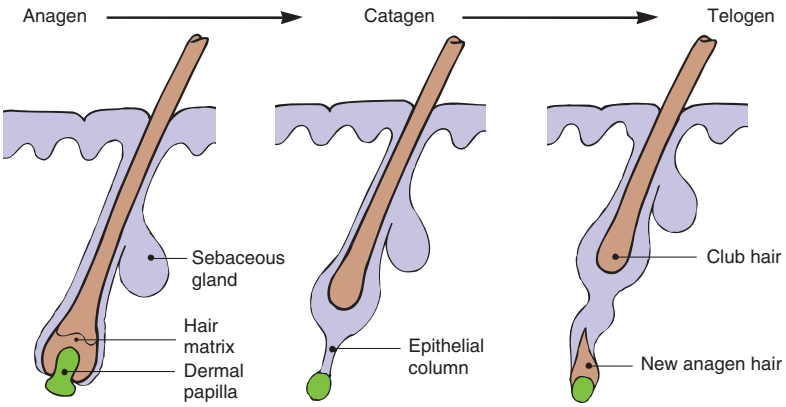


Fig. 3.2 The three phases of hair development.

Rate of maturation

Kinetic studies show that, on average, the dividing basal cells replicate every 200–400 h. The resultant differentiating cells in normal skin take 52–75 days to be shed from the stratum corneum. The epidermal transit time is considerably reduced in keratinization disorders such as psoriasis.

Hair growth

In most mammals, hair or fur plays an essential role in survival, especially in the conservation of heat; this is not the case in 'nude' humans. Scalp hair in humans does function as a protection against the cancer-inducing effects of ultraviolet (UV) radiation; it also protects against minor injury. However, the main role of hair in human society is as an organ of sexual attraction, and therein lies its importance to the cosmetics industry.

The rate of hair growth differs depending on the site. For example, eyebrow hair grows faster and has a shorter anagen (see later) than scalp hair. On average, there are about 100 000 hairs on the scalp, and the normal rate of growth is 0.4 mm/24 h. Hair growth is cyclical, with three phases, and is randomized for individual hairs, although synchronization does occur during pregnancy. The three phases of hair development (Fig. 3.2) are anagen, catagen and telogen.

1. *Anagen* is the growing phase. For scalp hair, this lasts from 3 to 7 years but, for eyebrow hair, it lasts only 4 months. At any one time, 80–90% of scalp hairs are in anagen, and about 50–100 scalp follicles switch to catagen per day.

Kinetic studies show that, on average, the dividing basal cells replicate every 200–400 h. The resultant differentiating cells in normal skin take 52–75 days to be shed from the stratum corneum. The epidermal transit time is considerably reduced in keratinization disorders such as psoriasis (Fig. e3.1).

(see Hair in Ch. 2).

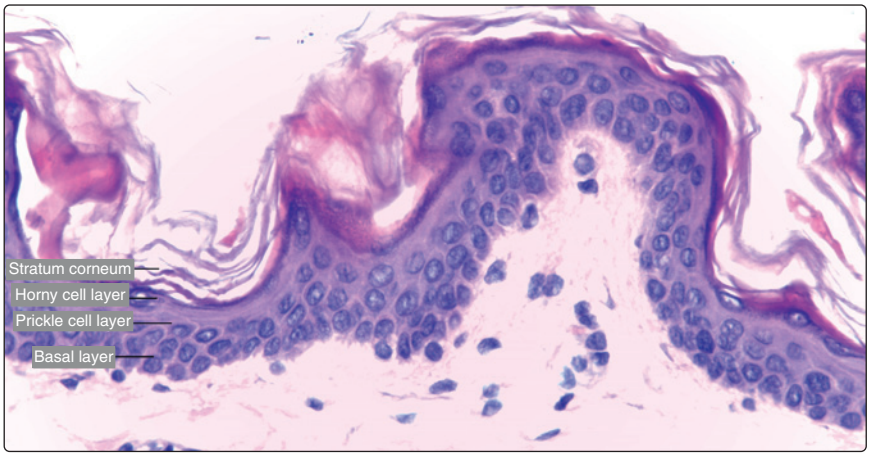


Fig. e3.1 Image of normal skin histology showing keratinocytes in epidermis.

2. *Catagen* is the resting phase and lasts 3–4 weeks. Hair protein synthesis stops, and the follicle retreats towards the surface. At any one time, 10–20% of scalp hairs are in catagen.
3. *Telogen* is the shedding phase, distinguished by the presence of hairs with a short club root. Each day, 50–100 scalp hairs are shed, with less than 1% of hairs being in telogen at any one time.

Melanocyte function

Melanocytes (located in the basal layer) produce the pigment melanin in elongated, membrane-bound organelles known as melanosomes (Fig. 3.3). These are packaged into granules, which are moved down dendritic processes and transferred by phagocytosis to adjacent keratinocytes. Melanin granules form a protective cap over the outer part of keratinocyte nuclei in the inner layers of the epidermis. In the stratum corneum, they are uniformly distributed to form a UV-absorbing blanket, which reduces the amount of radiation penetrating the skin. Thickening of the epidermis also blocks UV.

UV radiation – mainly the wavelengths of 290–320 nm (UVB) – darkens the skin first by immediate photo-oxidation of preformed melanin and second, over a period of days, by stimulating melanocytes to produce more melanin. UV radiation also induces keratinocyte proliferation, resulting in thickening of the epidermis.

Variations in racial pigmentation result not from differences in melanocyte numbers, but in the number and size of melanosomes produced. Gene polymorphisms in red-haired people cause impaired melanocyte-stimulating hormone signalling to the MC1-receptor, which leads to reduced levels of melanocyte eumelanin (brown/black) and therefore predominantly red phaeomelanin (p. 8).

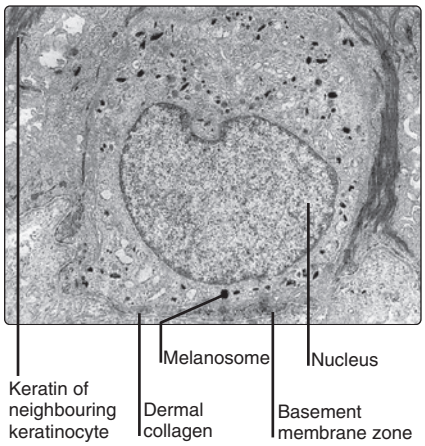


Fig. 3.3 Electron micrograph of a melanocyte.

Thermoregulation

The maintenance of a near-constant body core temperature of 37 °C is a great advantage to humans, allowing a constancy to many biochemical reactions that would otherwise fluctuate widely with temperature changes. Thermoregulation depends on several factors, including metabolism and exercise, but the skin plays an important part in control through the evaporation of sweat and by direct heat loss from the surface.

Blood flow

Skin temperature is highly responsive to skin blood flow. Dilatation or contraction of the dermal blood vessels results in vast changes in blood flow, which can vary from 1 to 100 mL/min per 100 g of skin for the fingers and forearms. Arteriovenous anastomoses under the control of the sympathetic nervous system shunt blood to the superficial venous plexuses (Fig. 3.4), affecting skin temperature. Local factors, both chemical and physical, can also have an effect.

Sweat

The production of sweat cools the skin through evaporation. The minimum insensible perspiration per day is 0.5 L. Maximum daily secretion is 10 L, with a maximum output of about 2 L/h. Men sweat more than women.

Sweating is not important for clearance of toxic substances but is important for barrier function. Watery isotonic sweat, produced in the sweat gland, is modified in the excretory portion of the duct to maintain the skin surface with:

- a pH of between 4 and 6.8
- a low concentration of Na^+ (30–70 mEq/L) and Cl^- (30–70 mEq/L)
- a high concentration of K^+ (up to 5 mEq/L), lactate (4–40 mEq/L), urea, ammonia and some amino acids.

Sweating may also occur in response to emotion and after eating spicy food. In addition to thermoregulation, sweat also helps to maintain the hydration of the horny layer and improves grip on the palms and soles.

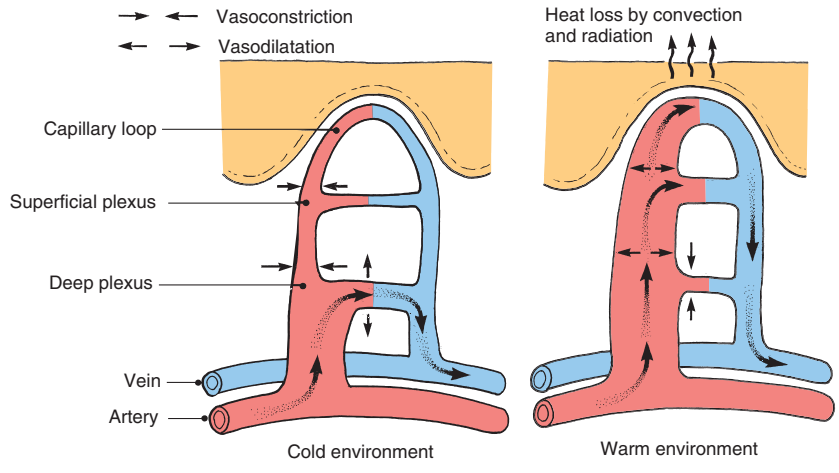


Fig. 3.4 Variations in blood supply to the skin under cold and warm conditions.

Physiology

- Basal cell replication rate: once every 200–400 h.
- Transepidermal cycle time: 52–75 days.
- Growth rate for scalp hair: 0.4 mm/24 h.
- Normal hair fall (scalp): 50–100/24 h.
- Fingernail growth: 0.1 mm/24 h (toenail is less).
- Skin blood flow is controlled by shunting at arteriovenous anastomoses.
- Minimum insensitive perspiration: 0.5 L/24 h.

Melanocytes derive from the neural crest and populate the epidermis in parallel with cutaneous nerves. Abnormal clones of melanocytes therefore often follow patterns consistent with dermatomal innervation (see Fig. 6.4; and Ch. 39 – Pigmentation).

Skin temperature is highly responsive to skin blood flow. Dilatation or contraction of the dermal blood vessels results in vast changes in blood flow, which can vary from 1 to 100 mL/min per 100 g of skin for the fingers and forearms. Arteriovenous anastomoses under the control of the sympathetic nervous system shunt blood to the superficial venous plexuses (Fig. 3.4 and Fig. e3.2), affecting skin temperature. Local factors, both chemical and physical, can also have an effect.

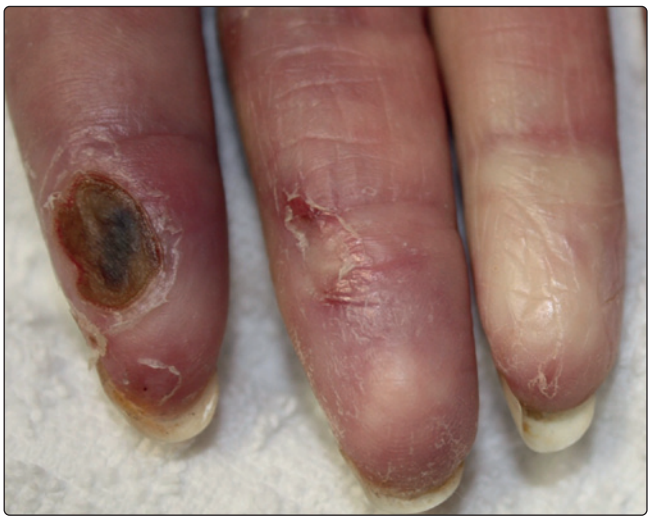


Fig. e3.2 Raynaud's syndrome reflects vascular spasm due to autoimmune disease, and demonstrates the change in skin appearance as a result of altered blood flow. A digital ulcer and tapering of the finger tips can be seen as a result of chronic arterial insufficiency in this case. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Further reading – online sources

Hill MA. 2016. Embryology Neural Crest – Melanocyte Development. Access via https://embryology.med.unsw.edu.au/embryology/index.php/Neural_Crest_-_Melanocyte_Development.

Further reading

Huggenberger, R., Detmar, M., 2011. The cutaneous vascular system in chronic skin inflammation. J. Investig. Dermatol. Symp. Proc. 15 (1), 24–32.

Milstone, L.M., 2004. Epidermal desquamation. J. Dermatol. Sci. 36, 131–140.

4 Biochemistry of the skin

Keratins

The important molecules synthesized by the skin include keratin, melanin, collagen and glycosaminoglycans.

Keratins are high-molecular-weight polypeptide chains produced by keratinocytes (Fig. 4.1). They are the major constituent of the stratum corneum, hair and nails. The stratum corneum comprises 65% keratin (along with 10% soluble protein, 10% amino acid, 10% lipid and 5% cell membrane).

Keratin proteins are of varying molecular weight (between 40 and 67 kDa). Different keratins are found at each level of the epidermis, depending on the stage of differentiation. Epidermal keratin contains less cystine and more glycine than the harder hair keratin.

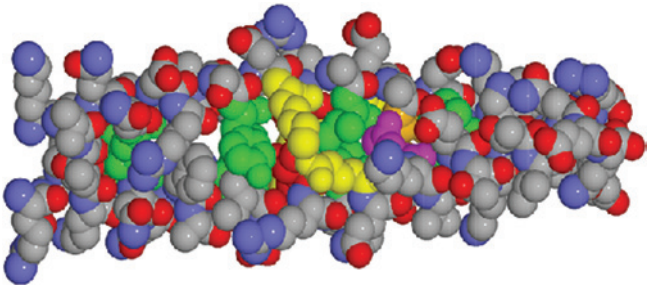


Fig. 4.1 Molecular structure of alpha-keratin. The molecule forms a helical coil which, if stretched, unwinds irreversibly to produce the beta form. The covalent bonds linking the cystine molecules provide extra strength. *(From J Invest Dermatol 2001; 116:964–969, with permission of Wiley Blackwell.)*

Melanins

Melanin is produced from tyrosine (Fig. 4.2) in melanocytes and takes two forms:

- *eumelanin*, which is more common and gives a brown–black colour
- *phaeomelanin*, which is less common and produces a yellow or red colour.

Most natural melanins are mixtures of eumelanin and phaeomelanin. Melanins act as an energy sink and as free radical scavengers, and absorb the energy of ultraviolet (UV) radiation.

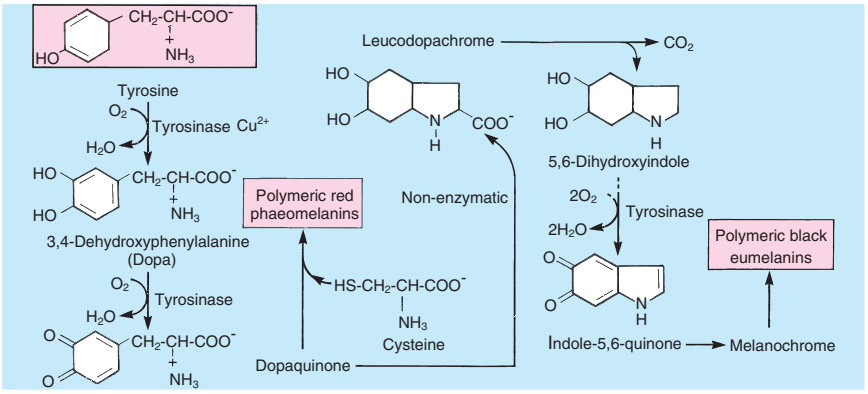


Fig. 4.2 Biosynthesis of melanin. Eumelanin is a high-molecular-weight polymer of complex structure formed by oxidative polymerization. The phaeomelanin polymer is synthesized from dopaquinone and cysteine (via cysteinyl DOPA).

Collagens

Collagens are synthesized by fibroblasts (Fig. 4.3) and are the major structural proteins of the dermis, forming 70–80% of its dry weight. The main amino acids in collagens are glycine, proline and hydroxyproline. Collagens are broken down, e.g. in wound healing, by collagenases, of which the matrix metalloproteinases are important. There are over 22 types of collagen; at least five are found in skin:

- *type I* – found in the reticular dermis
- *type III* – found in the papillary dermis
- *types IV* and *VII* – found in the basement membrane structures
- *type VIII* – found in endothelial cells.

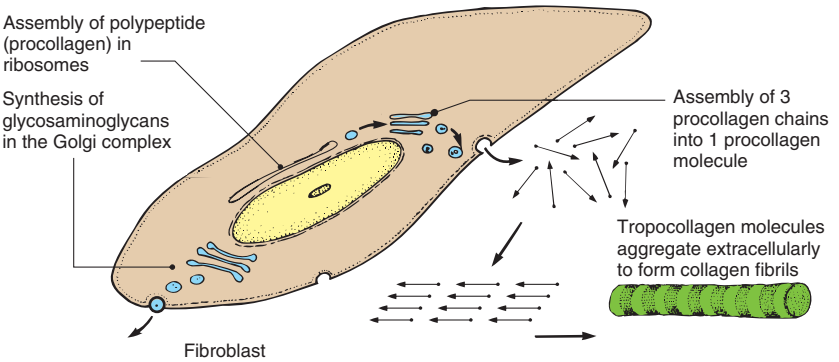


Fig. 4.3 Collagen production. Tropocollagen is formed from three polypeptide chains that are coiled around each other in a triple helix. Assembled collagen fibrils are 100 nm wide, with cross-striations visible with electron microscopy every 64 nm.

(see Table e1.1)
(see Melanocyte function in Ch. 3)
(see Table e1.1)

Glycosaminoglycans

The 'ground substance' of skin is largely made up of GAGs, providing viscosity and hydration. In the dermis, chondroitin sulphate is the main GAG, along with dermatan sulphate and hyaluronan.

GAGs often exist as high-molecular-weight polymers with a protein core. These structures are known as *proteoglycans* (Fig. 4.4).

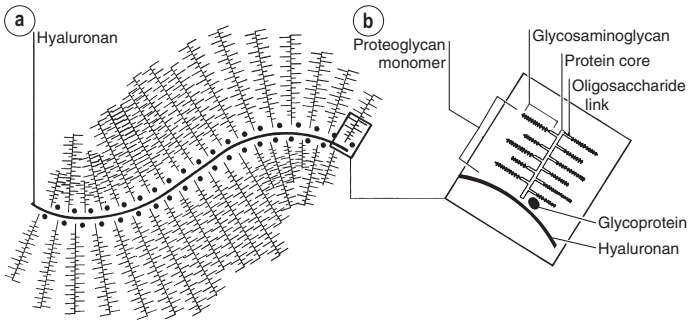


Fig. 4.4 Proteoglycan. (a) Proteoglycan aggregate with central filament of hyaluronan. (b) Detailed view of proteoglycan monomer with protein core.

Skin surface secretions

The skin surface has a slightly acidic pH (between 6 and 7). Sebum (Table 4.1), sweat and the horny layer (including intercellular lipid) contribute to the surface conditions, which generally discourage microbial proliferation.

Table 4.1 **Sebum and epidermal lipid composition**

Component	Sebum (%)	Epidermal lipid (%)
Glyceride/free fatty acid	58	65
Wax esters	26	0
Squalene	12	0
Cholesterol esters	3	15
Cholesterol	1	20

Subcutaneous fat

Triglyceride is synthesized from α-glycerophosphate and acyl coenzyme A (CoA). Triglyceride is broken down by lipase to give free fatty acid (FFA) – an energy source – and glycerol (Fig. 4.5).

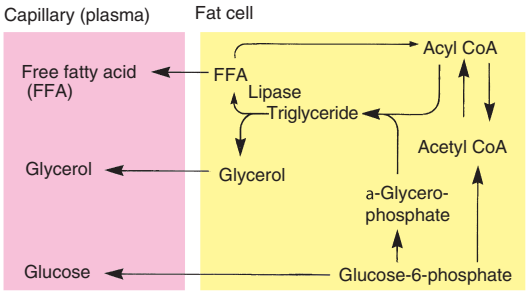
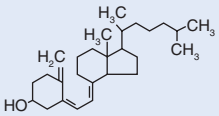
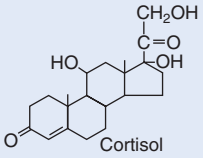


Fig. 4.5 Metabolism of subcutaneous fat.

Hormones and the skin

The skin is the site of production of vitamin D and epidermal growth factor, but it is a target organ for other hormones and is frequently affected in endocrine diseases (Table 4.2).

Table 4.2 **Hormones and the skin**

Hormone	Site of production	Effects
Vitamin D 	Skin (dermis). Produced from precursors through the action of UV radiation	Important for the absorption of calcium and for calcification
Corticosteroids 	Adrenal cortex	Receptors on several cells in both epidermis and dermis Produce vasoconstriction Reduce mitosis by basal cells Generate antiinflammatory effects on leucocytes Inhibit phospholipase A
Androgens	Adrenal cortex Gonads	Receptors on hair follicles and sebaceous glands Stimulate terminal hair growth and increased output of sebum
Melanocyte-stimulating hormone (MSH)	Pituitary gland (N-terminal peptide of adrenocorticotrophic hormone; ACTH)	Stimulates melanogenesis
Oestrogens	Adrenal cortex Ovaries	Stimulate melanogenesis
Epidermal growth factor (EGF)	Skin (probably produced at several sites inside, as well as outside, the skin)	Receptors found on keratinocytes, hair follicles, sebaceous glands and sweat duct cells Stimulates differentiation Alters calcium metabolism
Cytokines, chemokines and eicosanoids induce systemic and local effects	Skin cells (keratinocytes, dendritic cells, lymphocytes, etc.)	Effects on immune cell recruitment to the skin, inflammation and cell proliferation

Biochemistry

- **Keratins** are made up of polypeptide helical coils linked by covalent bonds. They form the horny layer, nails and hair.
- **Melanin** is a complex polymer synthesized from tyrosine. There are eu- and phaeo- types. Melanins absorb free radicals and energy including UV.
- **Collagens** are polypeptide polymers that constitute 75% of the dry weight of the dermis. They are synthesized by fibroblasts.
- **Glycosaminoglycans** make up the ground substance of skin. They provide viscosity and hydration, and can exist as high-molecular-weight polymers.
- **Vitamin D:** cutaneous UV activation produces the active form of vitamin D3 from the inactive 7-dehydrocholesterol via the precursor previtamin D3.
- **Androgen receptors** in hair/sebaceous glands make these structures sensitive to the androgen surge of puberty.

Further reading

Slominski, A., 2005. Neuroendocrine system of the skin. Dermatology 211 (3), 199–208.

5 Inflammation, immunity and the skin

Inflammatory responses are central to biological homeostasis. Inflammation is mediated by molecular signalling between resident skin cells and specialized immunological cells, which results in specific cellular interactions, or by release of soluble mediators. In the skin, strong inflammatory reactions are important for defence against infection (e.g. redness and exudate in impetigo), but in immunocompromised individuals, the risk of infection is increased (e.g. viral warts). As well as defence against infection, it is increasingly recognized that immunological responses are important in host defence against skin cancer, and that immunosuppression results in increased risk of all skin cancers, including squamous cell carcinoma and malignant melanoma. However, immune responses in the skin can also be detrimental to the host and when dysregulated, result in inappropriate responses against self-proteins (autoimmune diseases) or benign environmental antigens (allergic responses).

The immunological components of skin are similar to other epithelia and can be separated into innate and adaptive immune systems. Innate immunity is a key inflammatory immune response by cells sensing 'danger', and is principally mediated by keratinocytes. Equally, the generous blood and lymphatic supplies to the dermis are important channels through which immune cells can pass to or from, which are required for adaptive immunity that requires immunological priming and delivers immunological memory.

Microbiome

On the surface of the skin lies a complex population of bacteria and fungi, which make up the skin microbiome. The density and proportions of different species differ per body site, and are more similar at the same site between individuals, than at different sites in the same individual, which emphasizes the important environmental niches created by differences such as sweatiness, sebaceous secretions, flexural locations and hair-bearing sites. In each square centimetre of skin, it is estimated that one million bacteria exist, but most do not penetrate the epidermal barrier. These microbes provide important stimuli for innate immunity, and in the steady-state, these are important for maintaining skin barrier function.

Immunologically functional cells in the skin

Keratinocytes

Keratinocytes synthesize antimicrobial peptides, produce proinflammatory cytokines (especially IL-1) and express immune reactive molecules such as major histocompatibility complex (MHC) class I and II molecules on their surface. They signal to cutaneous dendritic cells and have been shown to be able to induce specific dendritic cells: T cell functional outcomes. For example, keratinocyte production of thymic stromal lymphopoietin (TSLP) induces dendritic cells to drive T cells towards an inflammatory Th2 phenotype.

Professional antigen presenting cells

The Langerhans cells (epidermis) and populations of dermal dendritic cells are the outermost sentinels of the cellular immune system (Fig. 5.1). Langerhans cells are dendritic and are characterized ultrastructurally by a unique cytoplasmic organelle known as the *Birbeck granule*. Recent work has shown the important role UV radiation plays in inducing photoimmunosuppression, which is mediated by effects on the skin dendritic cell population.

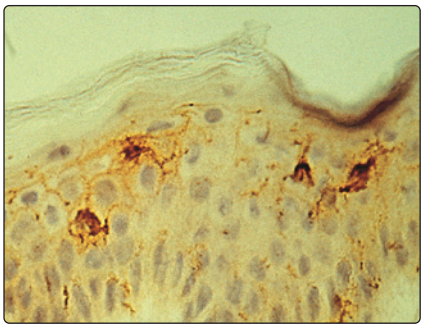


Fig. 5.1 Langerhans cell. The dendritic Langerhans cells form a network in the epidermis. In this section, the Langerhans cells have been stained with a monoclonal antibody to HLA-DR.

Lymphocytes

T lymphocyte (and probably B lymphocyte) migration to and from circulation through normal skin for immunosurveillance is regulated by lymphocyte surface molecules that promote 'skin homing', including cutaneous leucocyte antigen (CLA), CCR4, CCR6 and CCR10. Recent important work has shown that in healthy states, large numbers of T cells reside permanently in the skin (resident memory T cells) and actually outnumber those circulating in the blood. These cells are important for host defence against cutaneous infections such as herpes viruses. Epithelial danger signals induced by infection and inflammation increase cutaneous and endothelial expression of skin homing receptor ligands, thereby enhancing the influx of circulatory lymphocytes into the cutaneous compartment.

Different types of T cell with differing functions are recognized in the skin:

- $CD4^+$ function is classified by cytokine production (Fig. 5.2), which also determines how they regulate class-switching of B cells to IgG (Th1) or IgE (Th2) production.
- $CD8^+$ cells are capable of cytokine production (Tc1 and Tc2, etc.) and target cell killing mediated by granzyme B and perforin production.
- Others: NKT ($CD4^+$ or $CD8^+$ or double or nil expressing); innate lymphoid cells (ILC2); γδT cells.

Mast cells

Mast cells are principally known for their ability to degranulate and release histamine and other vasoactive molecules.

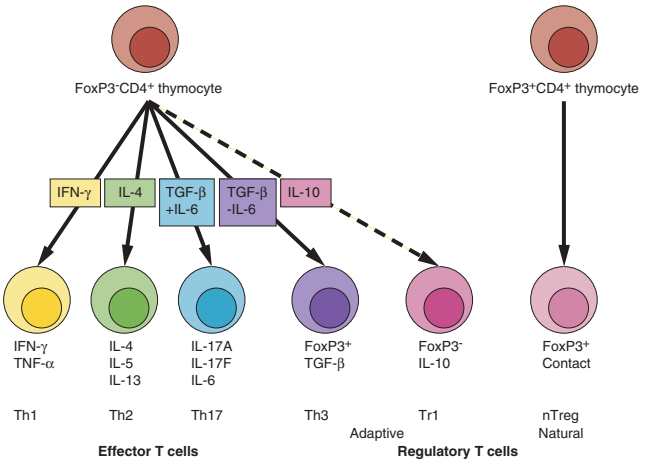


Fig. 5.2 $CD4^+$ T cell subsets. The cytokine/function polarization of $CD4^+$ T cells, which was until recently, limited to the Th1/Th2 paradigm, has been expanded. Cytokines that are critical to lineage development are indicated in the arrow boxes. Below the cells are the effector or regulatory cytokine repertoires of each cell type (nTreg are contact dependent) and their abbreviated names.

This is very rapid because the granules are preformed. Degranulation arises in response to cross-linking of the high-affinity IgE receptor. Cross-linking arises when IgE molecules on the surface of the receptors bind the same protein antigen. Mast cells also synthesize a wide range of cytokines, and experimental models support the concept that mast cells play an important role in skin immune responses. Mast cells are normal residents of the dermis, and their circulating counterparts are basophils. Mast cell numbers increase during inflammatory reactions.

Eosinophils

Eosinophils are richly packed with potent mediators of inflammation and cytokines important in regulation of Th2-type immune responses.

Complement

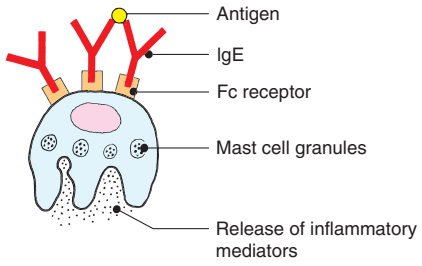
Activation of the complement cascade down either the classical or the alternative pathways results in molecules that have powerful effects. These include opsonization, lysis, mast cell degranulation, smooth muscle contraction and chemotaxis for neutrophils and macrophages.

Hypersensitivity reactions and the skin

'Hypersensitivity' is the term applied when an adaptive immune response is inappropriate or exaggerated to the degree that tissue damage results. The skin can exhibit all the main types of hypersensitivity response.

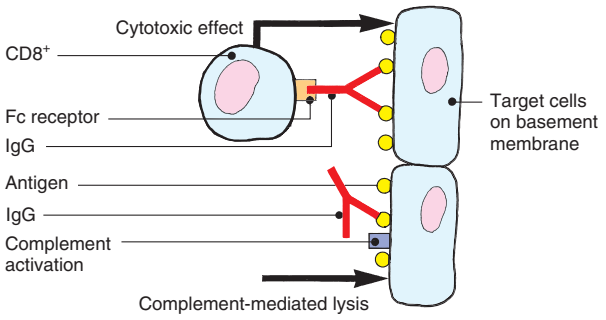
Type I (immediate)

Allergen-specific immunoglobulin (Ig) E bound to the surface of mast cells causes degranulation on antigen exposure (as discussed earlier). The result in the skin is urticaria, although massive histamine release can cause anaphylaxis. The response occurs within minutes, although a delayed component is recognized. Factors other than IgE can cause mast cell degranulation.



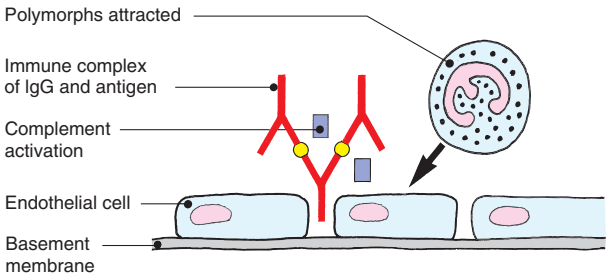
Type II (antibody-dependent cytotoxicity)

IgG antibodies directed against an antigen on target skin cells or structures induce cytotoxicity by killer T cells or by complement activation. For example, IgG pemphigus antibodies directed against desmoglein on the keratinocyte surface result in activation of complement, attraction of effector cells and lysis of the keratinocytes. Intraepidermal blisters result.



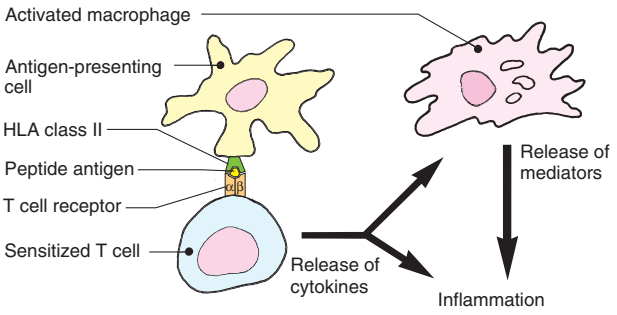
Type III (immune complex disease)

Immune complexes formed by the combination of antigen and IgG or IgM antibodies in the blood are deposited in the walls of small vessels, often those of the skin. Complement activation, platelet aggregation and the release of lysosomal enzymes from polymorphs cause vascular damage. This *leucocytoclastic vasculitis* is seen, e.g. with systemic lupus erythematosus and dermatomyositis, but also occurs with microbial infections such as infective endocarditis.



Type IV (cell-mediated or delayed)

Lymphocytes sensitized by cutaneous dendritic cells in the draining lymph node proliferate and undertake immunosurveillance of the tissues. On re-encounter with their cognate antigen–MHC complex, they become activated and induce inflammation and/or cell killing. From antigen exposure to sensitization takes 7–14 days. However, long-lived memory cells are able to undertake rapid expansion at a subsequent exposure and provide lasting immunity. Allergic contact dermatitis (p. 36) and the tuberculin reaction to intradermally administered antigen are both forms of type IV reaction. The responses to skin infections such as leprosy or tuberculosis are granulomatous variants of the reaction.



Immunology

- Resident microbes on the skin surface make up an important component to skin homeostasis.
- Skin provides a physical barrier to infection and possesses antimicrobial peptides.
- Dendritic cells in the skin, including epidermal Langerhans cells, form outposts of the cellular immune system and can present antigens to immunocompetent cells, e.g. T lymphocytes.
- T cells circulate through normal skin and form part of the skin-associated lymphoid tissue. They are localized by adhesion molecules.
- Keratinocytes can be immunologically active cells.
- All four types of hypersensitivity reaction occur in the skin.

Immunogenetics

The tissue-type antigens of an individual are found in the MHC, located in humans on the human leucocyte antigen (HLA) gene cluster on chromosome 6. The classical HLA genes are HLA-A, B and C (MHC class I) and DP, DQ and DR (MHC class II). The MHC class I complexes ($CD8^+$ restricted) are ubiquitously expressed, but MHC class II ($CD4^+$ restricted) is confined to professional antigen presenting cells (including B lymphocytes, Langerhans cells, dermal dendritic cells and macrophages). During inflammation, other cell types such as endothelial cells and keratinocytes can express MHC class II. There are specific HLA genes associated with an increased likelihood of certain diseases, some of which are 'autoimmune' in nature (Table e5.1).

T cell migration from the blood to the peripheral tissues is tightly regulated by surface molecule expression on T cells and the vascular endothelium (Fig. e5.1).

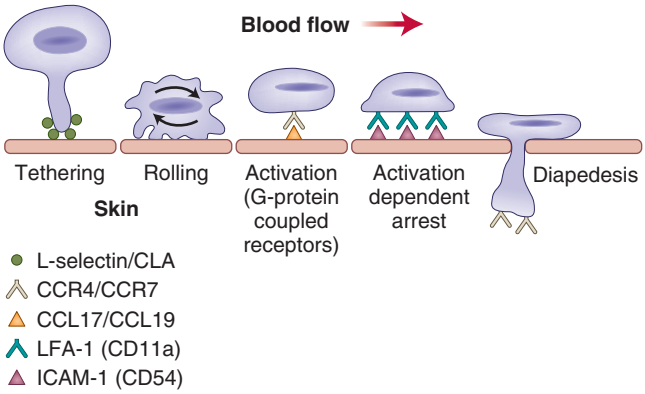


Fig. e5.1 T cell migration. The speed and timescale of lymphocyte interactions in the process of migration vary significantly. Example T cell-endothelial cell interactions are included. As the cell successfully tethers, its velocity slows dramatically during rolling, G-protein coupled activation occurs over seconds and arrest is reversible over minutes. Diapedesis takes approximately 10 min.

Table e5.1 **Skin disease associations of HLA antigens**

Disease	HLA antigen	Relative risk
Behçet's disease	B5	10
Dermatitis herpetiformis	B8	15
	DRw3	>15
Pemphigus	DRw4	10
Psoriasis	B13	4
	Dw7	10
	Cw6	12
Psoriatic arthropathy	B27	10
	Bw38	9
Reiter's disease	B27	35

6 Molecular genetics and the skin

Recent and rapid advances in genetics have had an impact on our understanding of skin diseases. The Human Genome Project has now mapped all human genes, of which there are about 35 000. Genetics has been found to be more complicated than the original Mendelian concept, and common conditions such as atopy occur as a result of a complex interaction between multiple susceptibility genes and the environment. An average pregnancy carries a 1% risk of a single gene disease and a 0.5% risk of a chromosome disorder, but genetically influenced traits, e.g. atopy, are much more common.

The human chromosomes

The human genome comprises 23 pairs of chromosomes that are numbered by size (Fig. 6.1). Chromosomes are packets of genes with support proteins in a large complex. The karyotype is an individual's number of chromosomes plus their sex chromosome constitution, i.e. 46XX for females and 46XY for males. The phenotype is the expression at a biological level of the genotype, e.g. blue eyes or atopy.

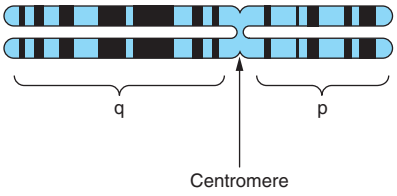


Fig. 6.1 Chromosome 2. Divided by the centromere into the shorter (p) and the longer (q) arms, showing banding with the Giemsa stain.

Genes and DNA

Common variations in DNA sequence found in a population are called 'genetic polymorphisms' and are inherited and not maintained by recurrent mutation. These polymorphisms may be functional (affect biological processes) or non-functional ('silent'). A new change or inherited alteration in DNA sequence that causes pathology (disease) is a mutation. Investigation of genetic causation of disease can be undertaken from a population/phenotype level down (genome screen – statistical association of gene sequence alterations in disease vs control group) or gene level up (candidate gene analysis – sequencing genes of interest in families or populations with disease vs control populations).

Molecular methods

DNA sequence variations can be identified by the consequent change in polymerase chain reaction (PCR) amplification product size (Fig. 6.2), loss or gain of restriction endonuclease cutting, or sequence analysis. In recent years, DNA sequencing has become a high-throughput technology that has led to the concept of 'whole genome sequencing' studies of healthy versus controls. As this technique is so powerful, smaller numbers are required and enormous advances in the identification of causative mutations for monogenic skin diseases have been made.

To establish which molecular pathways may be important in disease pathogenesis, gene chip arrays and 'next generation sequencing' allow detailed and quantitative analysis of the transcribed genes in a diseased tissue (transcriptome). The transcribed genes are subject to further regulation by RNA degradation, silencing and inhibition. Thus, study of the protein repertoire in the diseased tissue (proteomics) may also be undertaken.

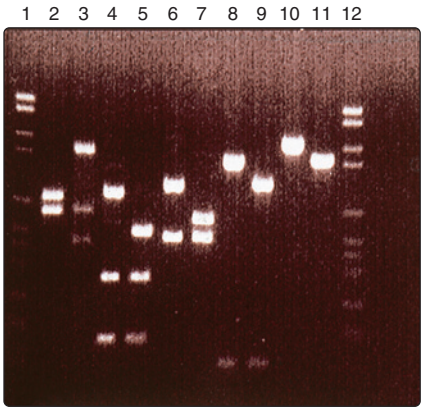


Fig. 6.2 Agarose gel electrophoresis, showing migration of DNA after cutting with enzymes, screening for mutations in a keratin gene.

Molecular techniques can be used to:

- detect small amounts of DNA, e.g. of human papilloma virus within a skin cancer
- sequence DNA from a 'candidate' section of an individual's chromosome and compare the base sequences with family members similarly affected by a disorder, thus mapping a specific gene polymorphism characteristic for that disease
- sequence the entire genome of an individual
- identify the repertoire of genes that have been transcribed as a measure of the protein profile of the cell.

Forms of inheritance

An individual with two different genes (alleles) at a particular locus is heterozygous, and one who has identical alleles is homozygous. Genes borne on chromosomes other than X and Y are autosomal, whereas those on X and Y are sex-linked. Factors governing genetic penetrance are unclear.

- *Dominant*. Affected individuals (both sexes) are h eterozygous for the gene; will have an affected parent (except for new mutations); and have a 50% chance of passing it to their children (Fig. 6.3).
- *Recessive*. An affected individual (of either sex) is homozygous for the gene, and both parents will be carriers and healthy. Consanguinity increases the risk. Recessive disorders are often severe. There is a 25% chance of heterozygotes passing the gene to the next generation.
- *X-linked recessive*. Only affects males, as females are healthy carriers.
- *X-linked dominant*. Affects males and females, although some disorders, e.g. incontinentia pigmenti, are lethal in males.
- *Mosaicism*. In mosaicism, an individual has two or more genetically different cell lines. The somatic (postconceptional) mutation of a single cell in an embryo results in a clone of subtly distinct cells. In the skin, this is revealed by the developmental growth pattern of Blaschko's lines (Fig. 6.4). Certain dermatoses, e.g. naevi and incontinentia pigmenti (Fig. 6.5), follow these lines, resulting in streaky or whorled patterns where the abnormal clone meets normal cells. A dermatomal distribution (Fig. 6.6) suggests nerve involvement.
- *Imprinting*. Imprinting involves the differential switching off of genes according to whether they have come from the father or the mother. It may be caused by methylation of DNA.

Inheritance of specific skin disorders

In psoriasis (p. 28) and atopic eczema (p. 38), a family history is common, but

DNA sequence variations can be identified by the consequent change in polymerase chain reaction (PCR) amplification product size (Fig. 6.2), loss or gain of restriction endonuclease cutting, or sequence analysis. In recent years, DNA sequencing has become a high-throughput technology that has led to the concept of 'whole genome sequencing' studies of healthy versus controls. As this technique is so powerful, smaller numbers are required and enormous advances in the identification of causative mutations for monogenic skin diseases have been made (Table e6.1).

Table e6.1 **Monogenic skin diseases**

Gene	Protein	Gene MIM no.	Disease	Inheritance
Ichthyoses				
ABCA12	ATP-binding cassette transporter 12	607800	Harlequin ichthyosis, autosomal recessive 4B	AR
ATP2A2	Sarcoplasmic/endoplasmic reticulum calcium ATPase 2	108740	Darier's disease	AD
ATP2C1	Calcium-transporting ATPase Type 2C, member 1	604384	Hailey–Hailey disease	AD
ERC2/3	ELKS/RAB6-Interacting/CAST family member 2/3	126340, 133510	Trichothiodystrophy	AR
FLG	Filaggrin	135940	Ichthyosis vulgaris	AD
RHBDF2	Rhomboid family member 2	614404	Tylosis with oesophageal cancer	AD
SPINK5	Serine protease inhibitor Kazal-type 5	6050101	Netherton syndrome	AR
Blistering disorders				
COL17A1	Collagen 17	113811	Epidermolysis bullosa, junctional, non-Herlitz type	AR
COL7A1	Collagen 7	120120	Epidermolysis bullosa dystrophica, autosomal recessive	AR
COL7A1	Collagen 7	120120	Transient bullous epidermolysis of the newborn	AD/AR
KRT14	Keratin 14	148066	Epidermolysis bullosa simplex, Dowling–Meara type	AD
DNA repair disorders				
XPA	Xeroderma pigmentosum, complementation group A	613208	Xeroderma pigmentosum, group A	AR
ERCC3	Excision repair cross-complementation group 3	133510	Xeroderma pigmentosum, group B	
RECQL4	RecQ protein-like 4	603780	Rothmund–Thompson syndrome	AR
Pigmentary disorders				
KIT	c-kit	164920	Piebaldism	AR
NF1	Neurofibromin 1	613113	Neurofibromatosis, type 1	AD
NF2	Neurofibromin 2	607379	Neurofibromatosis, type 2	AD
PTPN11	Tyrosine-protein phosphatase non-receptor type 11	176876	Leopard syndrome	AD
SPRED1	Sprouty-related, EVH1 domain containing 1	609291	Legius syndrome	AD
TYR	Tyrosinase	606933	Albinism, oculocutaneous, type 1 (A/B)	AR
Appendigeal and vascular disorders				
EDAR	Ectodysplasin A receptor	604095	Ectodermal dysplasia, hypohidrotic	AD
EDARADDEDAR-associated death domain		606603	Ectodermal dysplasia, hypohidrotic	AD
GNAQ	Guanine nucleotide-binding protein G(q)	600998	Sturge–Weber syndrome	mosaic
KRT81	Keratin 81	602153	Monilethrix	AD
KRT83	Keratin 83	602765	Monilethrix	AD
RASA1	RAS p21 protein activator 1	139150	Parkes–Weber syndrome	AD
Connective tissue disorders				
ABCC6	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	603234	Pseudoxanthoma elasticum	AR
COL1A1	Collagen 1, Alpha 1	120150	Ehlers–Danlos syndrome, type I/VIIA	AD
COL5A1	Collagen 5, Alpha 2	120215	Ehlers–Danlos syndrome, type I/II	AD
ELN	Elastin	130160	Cutis Laxa	AD
FBN1	Fibrillin 1	134797	Marfan syndrome	AD
Cancer syndromes				
AKT1	Protein kinase B alpha	164730	Cowden syndrome	AD
APC	Adenomatous polyposis coli	611731	Gardner syndrome	AD
FLCN	Folliculin	607273	Birt–Hogg–Dube syndrome	AD
PTCH1	Patched 1	601309	Gorlin syndrome	AD
TSC1	Tuberous sclerosis 1	605284	Tuberous sclerosis complex	AD
TSC2	Tuberous sclerosis 2	191092	Tuberous sclerosis complex	AD

Note: This is not an exhaustive list. Some diseases are associated with mutations in several genes as shown by hypohidrotic ectodermal dysplasia, monilethrix and tuberous sclerosis complex. Some gene mutations are associated with many diseases such as collagen 7A1, collagen 1A1 and collagen 5A1. Other diseases have variants, e.g. xeroderma pigmentosum groups A–G. Therefore, clinical description is critical and allows complete phenotype genotype correlation.
(Adapted from Lemke JR, Kernland-Lang K, Hörtnagel K, Itin P. 2014. Monogenic human skin disorders. Dermatology 229(2):55–64.)

- *Mosaicism*. In mosaicism, an individual has two or more genetically different cell lines. The somatic (postconceptional) mutation of a single cell in an embryo results in a clone of subtly distinct cells. In the skin, this is revealed by the developmental growth pattern of Blaschko's lines (Fig. 6.4). Certain dermatoses, e.g. naevi and incontinentia pigmenti (Fig. 6.5 and Fig. e6.1), follow these lines, resulting in streaky or whorled patterns where the abnormal clone meets normal cells. A dermatomal distribution (Fig. 6.6 and Fig. e6.2) suggests nerve involvement.

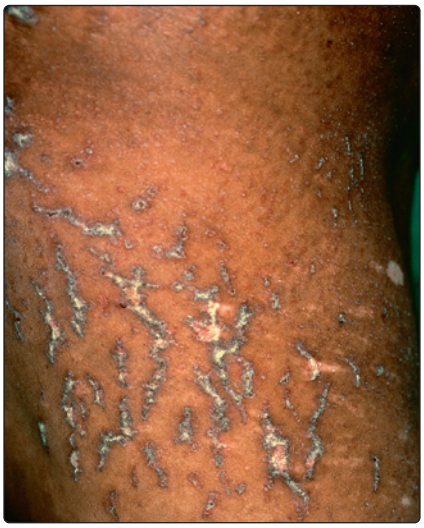


Fig. e6.1 Lichen striatus, lesion following lines of Blaschko. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

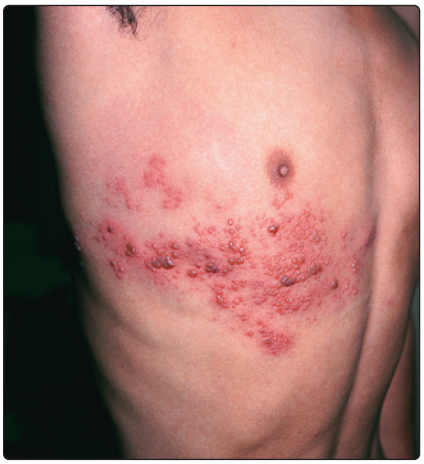


Fig. e6.2 Herpes zoster, classic dermatomal distribution. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

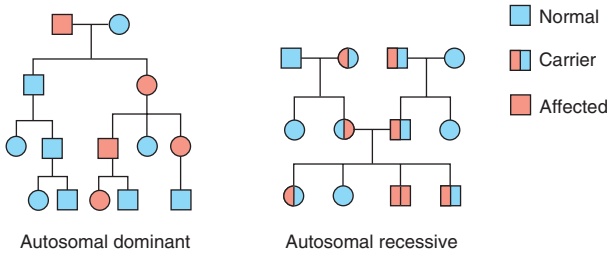


Fig. 6.3 Autosomal dominant and recessive patterns of inheritance.

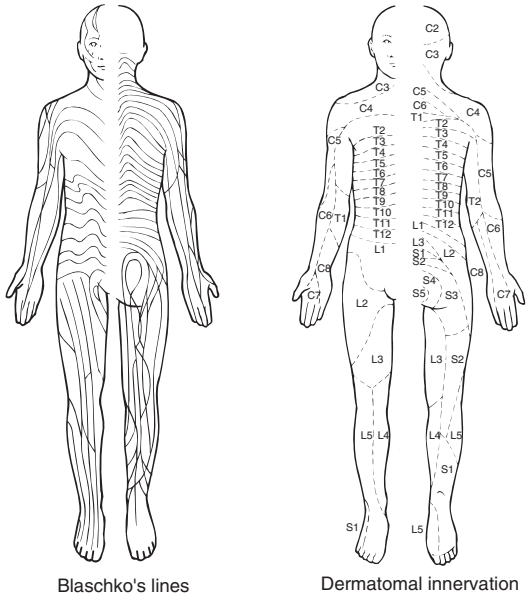


Fig. 6.4 Blaschko's lines represent the growth trends of embryonic tissue, whereas the dermatomes map out areas of skin innervation.

the exact mode of inheritance is unclear. Psoriasis may be inherited polygenically or by an autosomal dominant gene with incomplete penetrance. Atopic eczema has recently been shown to be strongly associated with chromosome 1q21 mutations in the gene encoding the epidermal protein, filaggrin. Inheritance patterns in the rarer conditions are often clearer (Table 6.1). Epidermolysis bullosa simplex and dystrophica (p. 94), the porphyrias (p. 88), the Ehlers–Danlos syndromes (p. 96) and some other conditions may be dominantly or recessively inherited.

Some dermatoses are associated with polymorphisms in the human leucocyte antigen (HLA) complex on chromosome 6 (p. 10). These tend to show polygenic inheritance and an association with autoimmunity.

Gene therapy

DNA-based prenatal diagnosis is possible in several genodermatoses (Table e6.1). Although recessive disorders in which there is a single gene defect offer scope for genetic treatment and gene therapy, which has been shown to be possible in epidermolysis bullosa, this remains a highly complicated and expensive process with potentially severe complications, including haematological malignancy.

Table 6.1 **The inheritance of selected skin disorders**

Inheritance	Disorder
Autosomal dominant	Darier's disease (p. 94) Dysplastic naevus syndrome (p. 102) Ichthyosis vulgaris (p. 94) Neurofibromatosis NF1 (p. 96) Palmoplantar keratoderma (p. 94) Peutz–Jeghers syndrome (p. 79) Tuberous sclerosis (p. 96)
Autosomal recessive	Acrodermatitis enteropathica (p. 89) Non-bullous ichthyosiform erythroderma (p. 94) Phenylketonuria (p. 78) Pseudoxanthoma elasticum (p. 97) Xeroderma pigmentosum (p. 97)
X-linked recessive	X-linked ichthyosis (p. 94)
X-linked	Incontinentia pigmenti (p. 13)

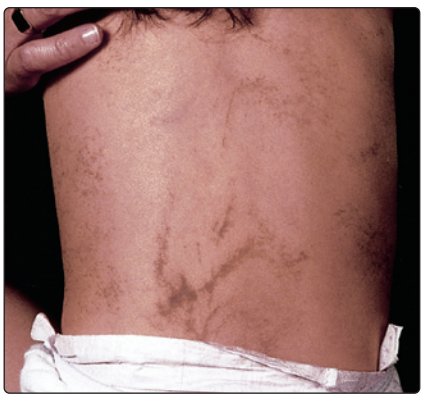


Fig. 6.5 Incontinentia pigmenti. Streaks and whorls follow the lines of Blaschko.

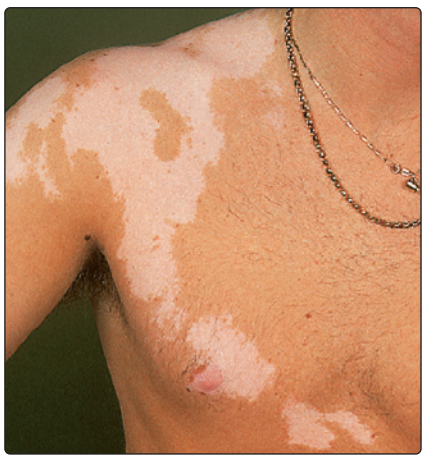


Fig. 6.6 Segmental vitiligo. Rather than follow Blaschko's lines, this occurs in a dermatomal distribution, suggesting a relationship with skin innervation.

Molecular genetics and the skin

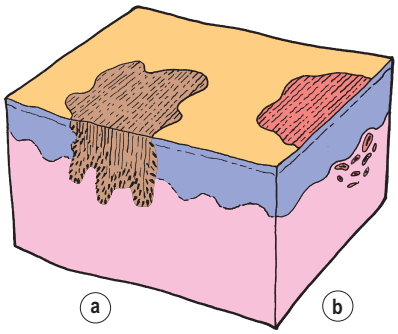
- The human genome of 23 chromosomes (karyotype 46XY or 46XX) contains 35 000 genes, all of which have been mapped. Additionally, mitochondria encode 37 genes for oxidative enzymes.
- DNA segments can be amplified by PCR and demonstrated by gel electrophoresis.
- Whole genome sequencing and microarray technology have advanced the molecular approach to studying disease pathogenesis.
- Dominant, recessive and X-linked inheritances are seen, but heredity is still unclear in several disorders.
- A dermatosis caused by mosaicism, due to a mutation producing more than one cell line, may appear in Blaschko's lines.
- Gene therapy should be possible for some recessive single gene disorders.

7 Terminology of skin lesions

Dermatology has a vocabulary that is quite distinct from that of other medical specialties and without which it is impossible to describe skin disorders (a skill vital in dermatologist training curricula). A *lesion* is a general term for an area of disease, usually small. An *eruption (*or *rash)* is a more widespread skin involvement, normally composed of several lesions, which may be the primary pathology (e.g. papules, vesicles or pustules) or due to secondary factors such as scratching or infection (e.g. crusting, lichenification or ulceration). Below is a selection of other commonly encountered dermatological terms. The online edition gives details of shapes of lesions and links to more examples.

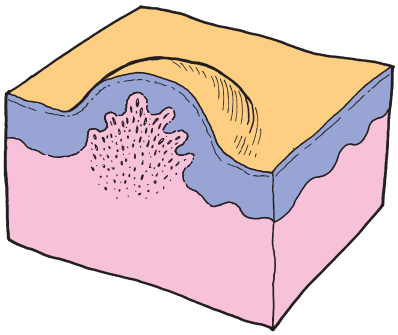
Macule (see Vitiligo, p. 78)

A macule is a localized area of colour or textural change in the skin. Macules can be hypopigmented, as in vitiligo; pigmented, as in (a) a freckle; or erythematous, as in (b) a capillary haemangioma.



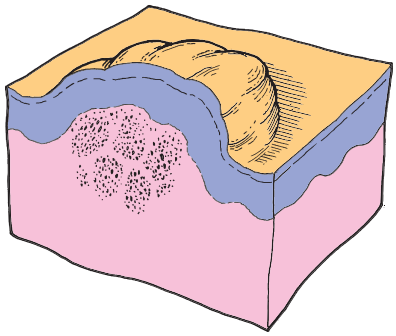
Papule (see Dermatofibroma, p. 99)

A papule is a small solid elevation of the skin, generally defined as <5 mm in diameter. Papules may be flat topped, as in lichen planus; dome-shaped, as in xanthomas; or spicular if related to hair follicles.



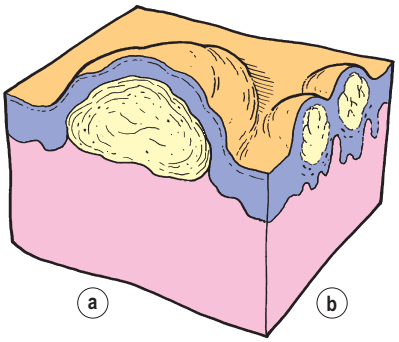
Nodule (see Squamous cell carcinoma, p. 107)

Similar to a papule but larger (i.e. >5 mm in diameter), nodules can involve any layer of the skin and can be oedematous or solid. Examples include a dermatofibroma (below) and secondary deposits.



Bulla (see Pemphigoid, p. 83)

A bulla is similar to a vesicle but larger: >5 mm in diameter. The blisters of bullous pemphigoid (a) and pemphigus vulgaris (p. 82) are examples.



Vesicle (see Dermatitis herpetiformis, p. 83)

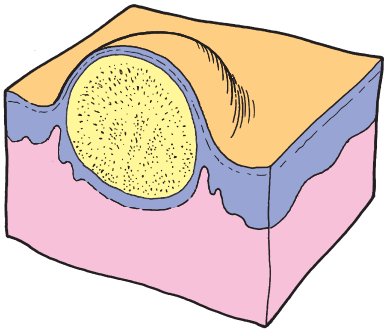
A vesicle is a small blister (<5 mm in diameter) consisting of clear fluid accumulated within or below the epidermis. Vesicles may be grouped as in dermatitis herpetiformis (subepidermal). Intraepidermal vesicles are shown in (b).

Glossary of other dermatological terms

- **Abscess:** A localized collection of pus formed by necrosis of tissue (Fig. 25.3).
- **Alopecia:** Absence of hair from a normally hairy area (Fig. 35.2).
- **Atrophy:** Loss of epidermis, dermis or both. Atrophic skin is thin, translucent and wrinkled with easily visible blood vessels (Fig. e11.2).
- **Burrow:** A tunnel in the skin caused by a parasite, particularly the Acarus of scabies (Fig. 33.5).
- **Callus:** Local hyperplasia of the horny layer, often of the palm or sole, due to pressure.
- **Carbuncle:** A collection of boils (furuncles) causing necrosis in the skin and subcutaneous tissues (Fig. 25.3).
- **Cellulitis:** A purulent inflammation of the skin and subcutaneous tissue (Fig. 26.5).
- **Comedo:** A plug of sebum and keratin in the dilated orifice of a pilosebaceous gland (Fig. 34.1).
- **Crust:** Dried exudate (normally serum, blood or pus) on the skin surface (Fig. 25.1).
- **Ecchymosis:** A macular red or purple haemorrhage, more than 2 mm in diameter, in the skin or mucous membrane (Fig. e11.2).
- **Erosion:** A superficial break in the epidermis, not extending into the dermis, which heals without scarring (Fig. 13.1).
- **Erythema:** Redness of the skin due to vascular dilatation (Fig. 34.4).
- **Excoriation:** A superficial abrasion, often linear, which results from scratching (Fig. 13.2).
- **Fissure:** A linear split in the epidermis, often just extending into the dermis (Fig. 19.3).
- **Folliculitis:** An inflammation of the hair follicles (Fig. 25.2).
- **Freckle:** A macular area in which there is increased pigment formation by melanocytes (Fig. 48.1).
- **Furuncle:** A pyogenic infection localized in a hair follicle (Fig. 25.2).
- **Gangrene:** Death of tissue, usually due to loss of blood supply.
- **Guttate:** Small drop-like lesions distributed in a 'shower', usually applied to a type of psoriasis (Fig. 14.4).

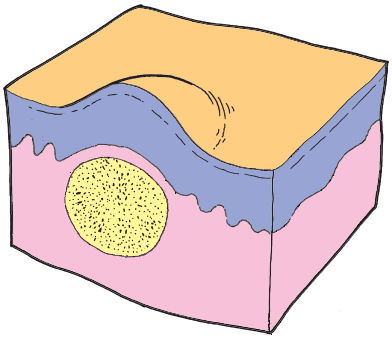
Pustule (see Acne, p. 68)

A pustule is a visible collection of free pus in a blister. Pustules may indicate infection (e.g. a furuncle), but not always, as pustules seen in psoriasis, for example, are not infected.



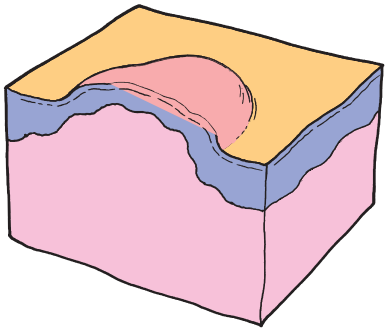
Cyst (see Acne, p. 68)

A cyst is a nodule consisting of an epithelial-lined cavity filled with fluid or semisolid material. An epidermal ('sebaceous') cyst is shown.



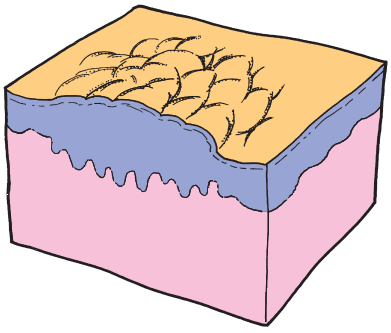
Wheal (see Urticaria, p. 80)

A wheal is a transitory, compressible papule or plaque of dermal oedema, red or white in colour and usually signifying urticaria.



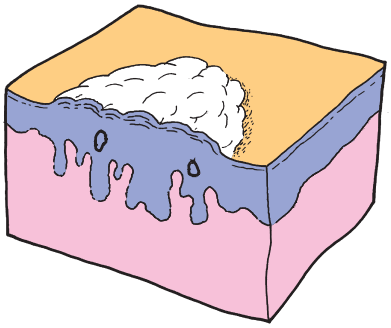
Plaque (see Psoriasis, p. 29)

A plaque is a palpable, plateau-like elevation of skin, usually >2 cm in diameter. Plaques are rarely over 5 mm in height and can be considered as extended papules. Certain lesions of psoriasis (below) and mycosis fungoides are good examples.



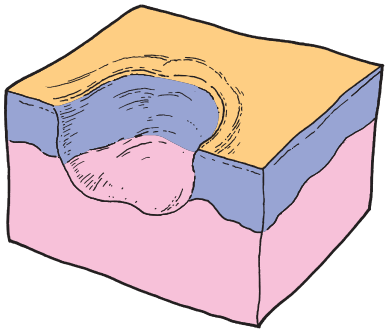
Scale (see Psoriasis, p. 29)

A scale is an accumulation of thickened, horny layer keratin in the form of readily detached fragments. Scales usually indicate inflammatory change and thickening of the epidermis. They may be fine, as in 'pityriasis'; white and silvery, as in psoriasis (below); or large and fish-like, as seen in ichthyosis.



Ulcer (see Venous leg ulcer, p. 76)

An ulcer is a circumscribed area of skin loss extending through the epidermis into the dermis. Ulcers are usually the result of impairment of the vascular or nutrient supply to the skin, e.g. as a result of peripheral arterial disease.



Glossary of other dermatological terms

- **Hirsuties:** Excessive male pattern hair growth (Fig. e35.2).
- **Hypertrichosis:** Excessive hair growth in a non-androgenic pattern (Fig. 35.4).
- **Keloid:** An elevated and progressive scar not showing regression (Fig. 49.6).
- **Keratoderma:** A horny thickening of the skin (Fig. 47.2).
- **Keratosis:** A horn-like thickening of the skin (Fig. 47.3).
- **Lichenification:** Chronic thickening of the skin with increased skin markings, as a result of rubbing or scratching (Fig. 9.2).
- **Milium:** A small white cyst containing keratin (Fig. e49.2).
- **Papilloma:** A nipple-like projection from the skin surface (Fig. 49.2).
- **Petechia:** A haemorrhagic punctate spot measuring 1–2 mm in diameter (Fig. e37.1a).
- **Poikiloderma:** A combination of hyperpigmentation, telangiectasia and atrophy seen together in a dermatosis (Fig. 42.1).
- **Purpura:** Extravasation of blood resulting in red discoloration of the skin or mucous membranes (Fig. 37.2).
- **Pyoderma:** Any skin disease that is purulent, i.e. discharging pus (Fig. 28.4).
- **Scar:** The replacement of normal tissue by fibrous connective tissue at the site of an injury (Fig. 14.2).
- **Sclerosis:** Diffuse or circumscribed induration of subcutaneous tissues, sometimes involving the dermis (Fig. 42.3).
- **Stria:** An atrophic linear band in the skin – white, pink or purple in colour. The result of connective tissue changes (Fig. 62.4).
- **Target lesion:** A lesion (<3 mm diameter) with three zones: a central area of dusky erythema or purpura, surrounded by a pale zone of oedema, with an outer ring of erythema (Fig. 43.2).
- **Telangiectasia:** Dilated dermal blood vessels giving rise to a visible lesion (Fig. 37.1).

Table e7.1 **Configuration of skin lesions**

Shape	Definition	Example
Arcuate	Incomplete circle	Urticaria, p. 80
Circinate	Ring-shaped outline	Types of balanitis, Fig. e64.3
Digitate	Like a finger's touch	Chronic superficial dermatitis, p. 110
Discoid	Filled circle	Discoid eczema, p. 40
Livedo	Criss-crossed chicken wire	Erythema ab igne, p. 75
Petaloid	Merged discoid lesion	Seborrhoeic dermatitis on the trunk, p. 45
Polycyclic	Merged or superimposed circles	Urticaria, p. 80
Reticulate	Lace-like pattern	Oral lichen planus, p. 42
Serpiginous	Snake-like tracks	Larva migrans, p. 65
Stellate	Star-shaped	Certain scars
Whorled	Swirling pattern	Incontinentia pigmenti, p. 13

The shapes of skin lesions can give a clue as to the diagnosis (see also Table e7.1).

Further reading – online sources

Further examples of the use of terminology to describe skin lesions can be found at the University of Wisconsin Department of Pediatrics website (access via http://www.pediatrics.wisc.edu/) and through Merck Manuals (as description of skin lesions; access via http://www.merckmanuals.com/).

Further reading – textbooks

Allen, H.B., 2009. Dermatology Terminology. Springer, Heidelberg.
Douglas, G., Nicol, F., Robertson, C. (Eds.), 2013. Macleod's Clinical Examination, thirteenth ed. Churchill Livingstone, Edinburgh.

8 Taking a history

The truism that 'there is no substitute for a good history' is just as applicable in dermatology as in any other branch of medicine. Indeed, history-taking is a core skill in the medical curriculum. The time needed to take a history depends on the complaint. For example, the history in a patient with hand warts can usually be completed quickly, but more time and detailed questioning are required for the patient with generalized itching.

History-taking in dermatology can be divided into five basic investigations: the presenting complaint, past medical history, social and occupational history, family history, and drug history.

Presenting complaint

Before any diagnosis, it is essential to find out when, where and how the problem started, what the initial lesions looked like and how they evolved and extended. Symptoms, particularly itching, the prime dermatological complaint, must be recorded along with any aggravating or exacerbating factors, such as sunlight. It is useful to gauge the effect of the eruption on the patient's ability to perform everyday tasks. For chronic conditions, it is helpful to assess the effect on the patient's quality of life and mental wellbeing. Specific scoring systems can record these effects, e.g. the Dermatology Life Quality Index or the Psoriasis Area Severity Index.

Case history 1

An 18-year-old male bank clerk developed a scaly erythematous plaque on the left elbow (Fig. 8.1) 6 months before presentation. It spread to involve the other elbow and both knees, but was not itchy. He developed scaliness in the scalp and nail dystrophy. His mother once had a similar rash.

Diagnosis: psoriasis (p. 28).

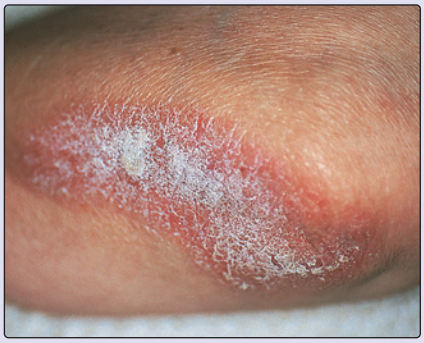


Fig. 8.1 Psoriatic plaque on the elbow.

Past medical history

Patients must be asked about any previous skin disease or atopic symptoms, such as hay fever, asthma or childhood eczema. Internal medical disorders may be relevant; these can involve the skin directly or may be associated with certain skin diseases. Prescribed or self-administered drugs may also cause an eruption. Dietary history is occasionally important, e.g. in some patients with atopic eczema (p. 38), but diet is often erroneously blamed for skin disease. Known allergies, and the nature of these, should be recorded.

Case history 2

A 29-year-old woman was referred from the department of respiratory medicine where she had recently been diagnosed as having pulmonary sarcoidosis. Three weeks previously, she had developed tender, warm erythematous nodules (Fig. 8.2) on the shins. She was on no medication. An incisional biopsy confirmed the clinical impression.

Diagnosis: erythema nodosum (p. 87).

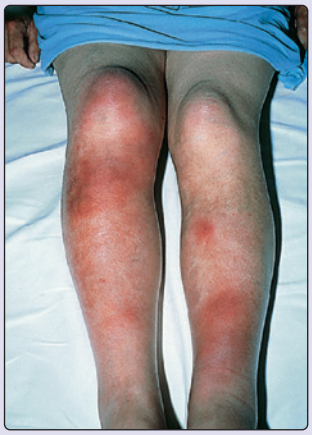


Fig. 8.2 Erythema nodosum on the lower legs. *(From Weller R, Hunter JAA, Savin J, Dah M, 2009, Clinical Dermatology, 4th edn. Wiley-Blackwell, with permission.)*

Social and occupational history

Many social factors can cause, influence or be influenced by a patient's skin complaint. Occupational exposures can induce contact dermatitis or other skin changes, and it is often necessary to ask the patient to explain exactly what he or she does at work. If the eruption improves when the patient is away from work, occupational factors should be suspected. Hobbies may also involve contact with objects or chemicals that could produce contact dermatitis.

Knowledge of the patient's living conditions and home background can be helpful in understanding a problem and deciding on treatment. Alcohol intake should be noted (especially if the use of potentially hepatotoxic drugs is being considered), as well as other factors. Living or travelling in warm climates potentially exposes an individual to a wide range of tropical and subtropical infections, and to strong sunlight.

Case history 3

A 45-year-old male printer engineer gave a 6-month history of hand dermatitis (Fig. 8.3). A few months previously, he had started to use the solvent trichloroethylene in his job. Patch testing was negative. On substituting a different solvent, the eruption cleared.

Diagnosis: irritant contact dermatitis (p. 34).

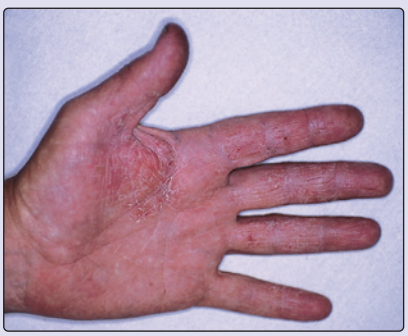


Fig. 8.3 Irritant contact dermatitis on the palm of the hand.

Family history

A full family history is essential. Some disorders with prominent skin signs are genetically inherited, e.g. tuberous sclerosis. Others, such as psoriasis or atopic eczema, have a strong hereditary component. In addition to genetic syndromes, a family history may reveal that other family members have had a recent onset of an eruption similar to that of the patient, suggesting an infection or infestation. It is sometimes also necessary to enquire about sexual contacts.

Case history 4

An 18-year-old male student gave a 3-month history of an intensely itchy papular eruption affecting the hands, wrists and penis (Table 8.1). Several lesions were excoriated (Fig. 8.4). Treatment with a potent topical steroid was of little benefit. His girlfriend had also recently developed itchy lesions. Close examination showed burrows in the skin.

Diagnosis: scabies (p. 67).

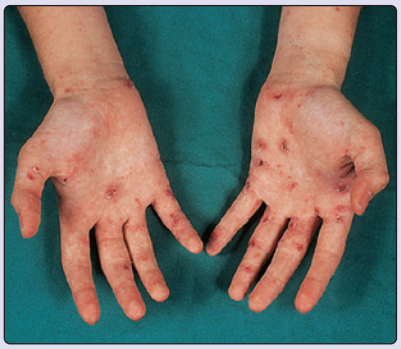


Fig. 8.4 Excoriated lesions of scabies.

Case history 5

A 25-year-old female sales assistant complained of brownish macules over her back (Fig. 8.5) and chest, which had first appeared in childhood and had gradually increased in number and size. During her teens, she had developed several soft pinkish, painless nodules on the trunk, some of which had become pedunculated. Her father had developed a few similar nodules in later life, and one of her two brothers had brown patches on his skin.

Diagnosis: von Recklinghausen's neurofibromatosis (NF-1; p. 96).

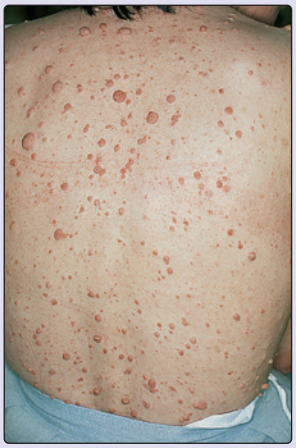


Fig. 8.5 Multiple neurofibromas on the back.

Table 8.1 **Itchy eruption: diagnosis**

Symptom	Possible diagnosis
Intensely itchy eruption	Scabies
	Lichen planus
	Dermatitis herpetiformis
	Urticaria
	Eczema
	Insect bites

Drug history

Both prescribed and self-administered medicaments can result in a 'drug eruption'. Almost all patients try an over-the-counter topical preparation (or a friend's or relative's cream) on rashes, and many have had a variety of treatments prescribed that may be inappropriate or may cause irritant or allergic reactions. It is important to quiz the patient about all medicament use, including the use of over-the-counter tablets or creams that the patient may well not think relevant.

Cosmetics, cleansing wipes and moisturizing creams can cause dermatitis, and it is often necessary to ask specifically about their use.

Case history 6

A 68-year-old woman had a minor irritating eruption on her forehead. She applied an antihistamine-containing cream that she bought in a pharmacy. Within 24 hours of applying it, her face became severely swollen (Fig. 8.6). Patch testing carried out later showed an allergic reaction to the cream.

Diagnosis: medicament dermatitis (p. 36).

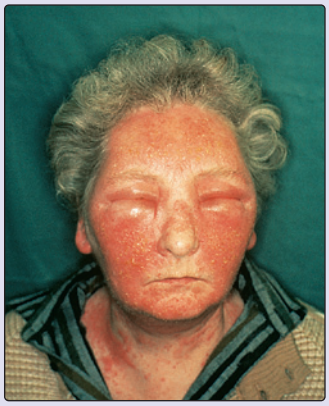


Fig. 8.6 Acute allergic contact dermatitis to a topical antihistamine cream.

Case history 7

An 18-year-old female secretary was given griseofulvin for a fungal infection. She went sunbathing and, 12 hours later, developed an eruption with a distribution in light-exposed areas (Fig. 8.7).

Diagnosis: phototoxic drug eruption (p. 90).

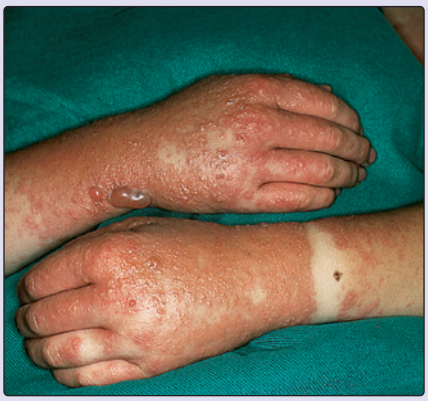


Fig. 8.7 Acute phototoxic drug eruption.

Taking a history

- Elicit the nature and temporal course of the eruption or lesion.
- Enquire about atopic symptoms, general medical conditions and foreign travel.
- Take a social, occupational and family history – it may be relevant. Ask about eczema or psoriasis in relatives.
- Identify any influence of the illness on day-to-day functions, including work.
- Record the recent use of drugs and medications, including topical agents.
- Ask about the use of cosmetics and, in relevant cases, exposure to sun or ultraviolet radiation (e.g. sunbeds).

Further reading – online sources

For an excellent generic guide on taking a general medical history, see: The University College London (search as History and Examination Guide, access via http://www.ucl.ac.uk/pcph/). For taking a dermatologically orientated history, see the 'Fastbleep' website (access via http://www.fastbleep.com/).

YouTube provides an audio guide with some slides from Dr Ian McColl of the Australian Institute of Dermatology, on taking a dermatological history. The Australian College of Rural and Remote Medicine provides a short video on taking a dermatological history, orientated towards skin cancer; also on YouTube.

The British Association of Dermatologists publishes (as a pdf) an excellent guide to taking a dermatological history and using the vocabulary of skin disease. 'Dermatology: A Handbook for Medical Students and Junior Doctors', 2nd edn. 2014, by NYZ Chiang and J Verbov, is available through the Association's website (access via http://www.bad.org.uk).

Further reading – textbooks

Douglas, G., Nicol, F., Robertson, C. (Eds.), 2013. Macleod's Clinical Examination, thirteenth ed. Churchill Livingstone, Edinburgh.

Lipoff, J., 2015. Dermatology Simplified: Outlines and Mnemonics. Springer, Heidelberg.

9 Examining the skin

The skin needs to be examined in good, preferably natural, light. The whole of the skin should be examined, ideally. This is essential for atypical or widespread eruptions (Fig. 9.1). Looking at the whole skin often reveals diagnostic lesions that the patient is unaware of or may think unimportant. In the elderly, thorough skin examination often allows the early detection of unexpected but treatable skin cancers.

Skin examination is difficult for the non-dermatologist, and the novice needs a pattern to follow. It is important to:

- note the distribution and colour of the lesions
- examine the morphology of individual lesions, their size, shape, border changes and spatial relationship; touch the skin – palpation reveals the consistency of a lesion
- assess the nails, hair and mucous membranes, sometimes in combination with a general examination (e.g. for lymphadenopathy)
- wear gloves when examining the mouth, genitals and perineum or if lesions may be infected
- use special techniques, e.g. dermoscopy, microscopy of scrapings to look for fungal elements, or the use of Wood's (ultraviolet A) light, where applicable.

Skin examination is a core curriculum skill, as is the ability to present one's findings (see online resources).

Distribution of eruption or lesions

Stand back from the patient and observe the pattern of the eruption (Fig. 9.1). Determine whether it is localized (e.g. a tumour) or widespread (e.g. a rash). If the latter, determine whether the eruption is symmetrical and, if so, peripheral or central. Note whether it involves the flexures (e.g. atopic eczema) or the extensor aspects (e.g. psoriasis). Is it limited to sun-exposed areas? Is it linear?

Dermatomal patterns are also seen. Herpes zoster (shingles) is the commonest example of this, but some naevi also appear in this guise or follow Blaschko's lines (p. 13). Regional patterns (see Fig. 9.1), e.g. involvement of the groin or axilla, will suggest certain diagnoses to the experienced physician. For example, guttate psoriasis and tinea versicolor tend to occur on the trunk, whereas lichen planus often occurs around the wrists, and contact dermatitis frequently affects the face, feet or hands. The factors resulting in these patterns are complex but include skin anatomy, e.g. blood vessels, nerves, appendages or embryonic lines, and environment, e.g. moist conditions in the axillae, contact with cosmetics, clothes or work materials, and sun exposure.

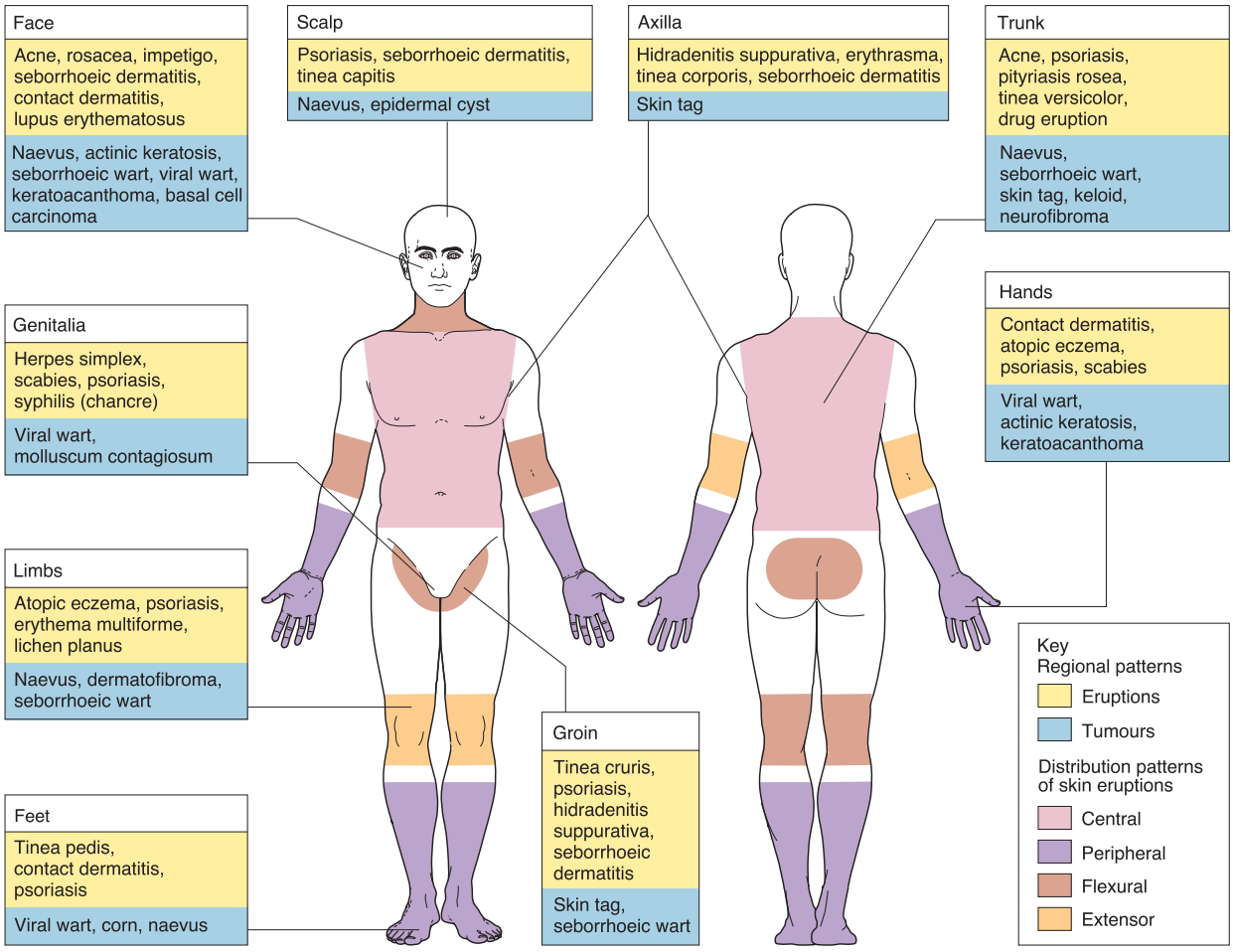


Fig. 9.1 Regional dermatology.

Case history 1

An 8-year-old girl gave a 12-month history of an itchy eruption affecting the antecubital and popliteal fossae (Fig. 9.2). Her mother had had a similar rash as a child. The pattern and the morphology were characteristic.

Diagnosis: atopic eczema (p. 38).

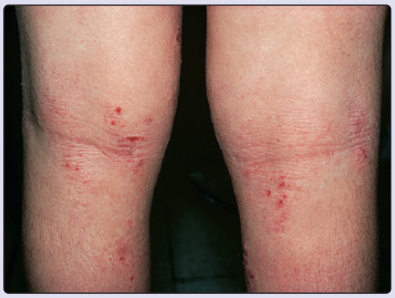


Fig. 9.2 Atopic eczema affecting the popliteal fossae.

Case history 2

Six weeks ago, a 25-year-old man developed a slightly itchy linear area running down the medial aspect of his left leg (Fig. 9.3). Dermatological conditions giving a linear eruption include lichen planus, morphoea, psoriasis and linear epidermal naevus.

Diagnosis: lichen striatus, a self-limiting inflammatory dermatitis of unknown origin.

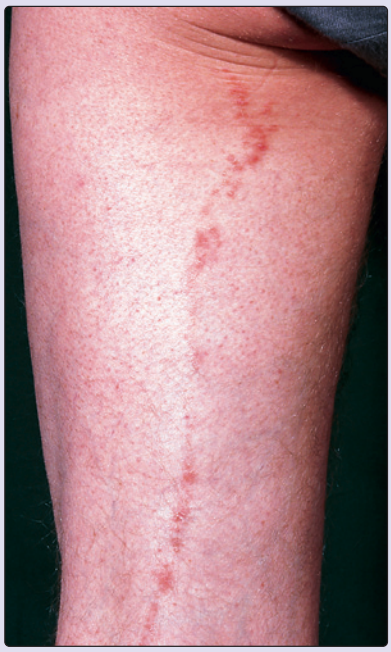


Fig. 9.3 Lichen striatus affecting the left leg.

Morphology of individual lesions

A dermoscope or hand lens is often helpful in looking at individual lesions. Palpation (often neglected by medical students) is also important to determine the consistency, depth and texture. Definitions of lesions are given on pages 14–15.

Lesions may be monomorphic (e.g. guttate psoriasis) or pleomorphic (e.g. chickenpox). There may also be secondary changes on top of primary lesions. The local configuration of lesions is often of diagnostic help (Table 9.1). Determine whether the lesions are grouped, linear or annular, or if they show the Koebner phenomenon (p. 28), whereby lesions appear in an area of trauma which is often linear, e.g. a scratch.

Table 9.1 **Configuration of lesions**

Configuration	Disease
Linear	Psoriasis, lichen striatus, linear epidermal naevus, lichen planus, morphoea
Grouped	Dermatitis herpetiformis, insect bites, herpes simplex, molluscum contagiosum
Annular	Tinea corporis (ringworm), mycosis fungoides, urticaria, granuloma annulare, annular erythemas
Koebner phenomenon	Lichen planus, psoriasis, viral warts, molluscum contagiosum, sarcoidosis, vitiligo

Nails, hair and mucous membranes

The nails, scalp and hair frequently show diagnostic and even pathognomonic signs (pp. 70–73). With any unusual or atypical eruption, the mucous membranes of the mouth and genitalia may show important changes, such as oral involvement by Wickham's striae in lichen planus, oral lesions in Kaposi's sarcoma or vulval involvement with lichen sclerosus.

General examination

Palpation of lymph nodes is important in patients with skin malignancy. In patients with a skin lymphoma, a full examination is needed, looking particularly for lymphadenopathy and hepatosplenomegaly. Palpation of pedal pulses is vital in patients with leg ulcers.

Special techniques and assessment of disease morbidity

The diagnoses of many skin conditions can be helped by special techniques, detailed on page 20. Photography is often used to record the state of a patient's skin disease and allows comparisons at follow-up visits.

Modern management of skin disease often requires the scoring of disease severity and impact for the initiation and monitoring of certain drugs. For example, the National Institute for Health and Clinical Excellence (NICE) states that a patient's psoriasis must be of a specified severity, according to the psoriasis area and severity index, before a biologic agent can be started (p. 32).

- **Psoriasis Area and Severity Index** (PASI). The PASI is a numerical score of the extent and activity of psoriasis, based on surface area and cutaneous features.
- **Dermatology Life Quality Index** (DLQI). The DLQI is a measure of the impact of a skin disease on a patient's social, work and personal activities over the preceding week.
- **Severity Scoring for Atopic Dermatitis** (SCORAD). The SCORAD gives a numerical value to the severity of a patient's atopic eczema.

Examining the skin

- Examine the entire skin surface.
- Use a dermoscope (p. 20) or a hand lens with good illumination.
- Gently palpate lesions to assess texture.
- Look at the nails, hair and mucous membranes (oral and genital).
- Observe for distribution, individual lesion morphology and configuration.
- Use scoring systems where indicated.
- Send scrapings for culture if a fungal infection is a possibility.

Scoring systems for skin diseases

There has been a proliferation of scoring systems for a wide variety of diseases over the last decade. Within Dermatology, the PASI, DLQI and SCORAD are widely used, but there are scoring systems for other diseases such as systemic sclerosis, acne and vitiligo.

Psoriasis area and severity index (PASI)

The PASI is now an essential tool for treatment guidance and disease monitoring in specialized psoriasis clinics; see guidelines on the treatment of psoriasis which can be accessed through the website of the Jordan University of Science and technology (access via http://www.just.edu.jo/).

An explanation of what the PASI is and how it is derived can be located at the PASI Training website (access via http://www.pasitraining.com).

An online interactive calculator is available: http://pasi.corti.li/ and also a downloadable template, which can be found under PASI on the website of the British Association of Dermatologists (access via http://www.bad.org.uk/).

The PASI and DLQI scores are important tools in the algorithm for the prescribing of biologic drugs, which can be found at the website of NICE (access via http://www.nice.org.uk/).

Dermatology life quality index (DLQI)

The DLQI is widely used to assess the impact of a wide variety of skin diseases on an individual. Instructions on the use of the DLQI can be found on the website of Cardiff University where the index was developed (access via http://www.cardiff.ac.uk/dermatology/), and a downloadable template is available from the British Association of Dermatologists (access via http://www.bad.org.uk/).

The National Institute for Clinical Excellence (NICE) requires, in the UK, a DLQI score of 15 or more before the retinoid drug alitretinoin can be prescribed for severe hand dermatitis (access via http://www.nice.org.uk/).

Severity scoring for atopic dermatitis (SCORAD)

The SCORAD is a useful marker for disease activity in atopic eczema, located under 'atopic eczema in children' at the NICE website (access via http://www.nice.org.uk/). More details and a downloadable template are available searching 'SCORAD' at the website of the Fondation Dermatite Atopique (access via http://www.fondation-dermatite-atopique.org/).

Further reading – online sources

The American Academy of Dermatology has various guides on dermatological examination (search as The skin exam, access via https://www.aad.org/).

Procedures for examining the skin are covered by videos on YouTube. There is one from the University of Queensland Certificate in Primary Care Skin Cancer Medicine, and another from Bates' Visual Guide to Physical Examination, 4th edn.

Further reading – textbooks

Douglas, G., Nicol, F., Robertson, C. (Eds.), 2013. Macleod's Clinical Examination, thirteenth ed. Churchill Livingstone, Edinburgh.

Lipoff, J., 2015. Dermatology Simplified: Outlines and Mnemonics. Springer, Heidelberg.

10 Practical clinic procedures

Dermatologists make use of several diagnostic and therapeutic procedures in their everyday clinical practice.

Diagnostic procedures

The ability to diagnose a skin disease is improved by the use of better methods of observing lesions and by appropriate use of samples for laboratory investigation. Patch tests and prick tests are described on pages 36–37 and 134.

Dermoscopy

A hand lens helps when looking at small lesions such as nits on hair shafts (Fig. 10.1) or scabetic burrows, but dermoscopy gives added information, especially for pigmented lesions. Dermoscopy employs a ×10 magnification illuminated lens system, which can visualize a lesion after the application of a drop of oil or water between the skin and the applied lens. Detailed visualization of the epidermal structures is possible, particularly the pigment network (Fig. 10.2). Analysis takes account of:

- the symmetry of the lesion
- patterns of pigmentation
- blue–white structures in the pigment network.

Dermoscopy allows an opinion to be made about the nature and malignant potential of the lesion.

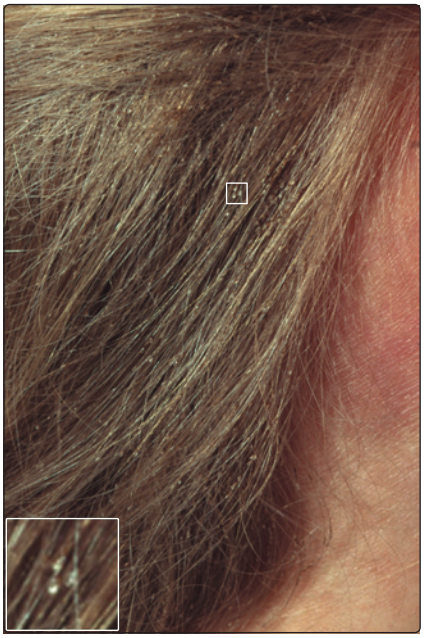


Fig. 10.1 Head lice and nits are evident on a hair shaft. Best visualized using a hand lens.

Microbiology samples

Swabs for bacterial and viral culture should be sampled from areas showing pus or exudation. Scrapings for fungal microscopy and culture are obtained by the following techniques:

- The active scaly edge of an eruption is sampled using a disposable scalpel blade held vertically to the skin.
- Nail samples are taken from the distal portion or from debris beneath the nail using clippers or a scalpel.
- Hair sampling requires plucking of hairs as the hair root is often infected (a scalp scraping is also worthwhile).

Samples are taken onto a small sheet of black paper or a microscope slide (Fig. 10.3). Direct microscopy of scrapings mounted in 20% potassium hydroxide solution will show hyphae (Fig. 10.4).

Demonstrating the acarus of scabies

Dermatologists sometimes need to demonstrate the mite to themselves or their patients (p. 67). This can be achieved by:

- removing the acarus using a small needle (the end of the burrow with the mite in can be difficult to see) and mounting it on a microscope slide
- visualizing the acarus by dermoscopy; it appears as a dark triangle
- taking a superficial scalpel scraping, which is examined by microscopy.

Wood's light examination

Wood's light is a hand-held ultraviolet A (UVA) source that can be shone on the skin in a darkened room to diagnose certain skin diseases that show particular patterns of fluorescence in UV radiation. It is used especially for:

- determining the extent of vitiligo
- showing hypopigmented macules in tuberous sclerosis

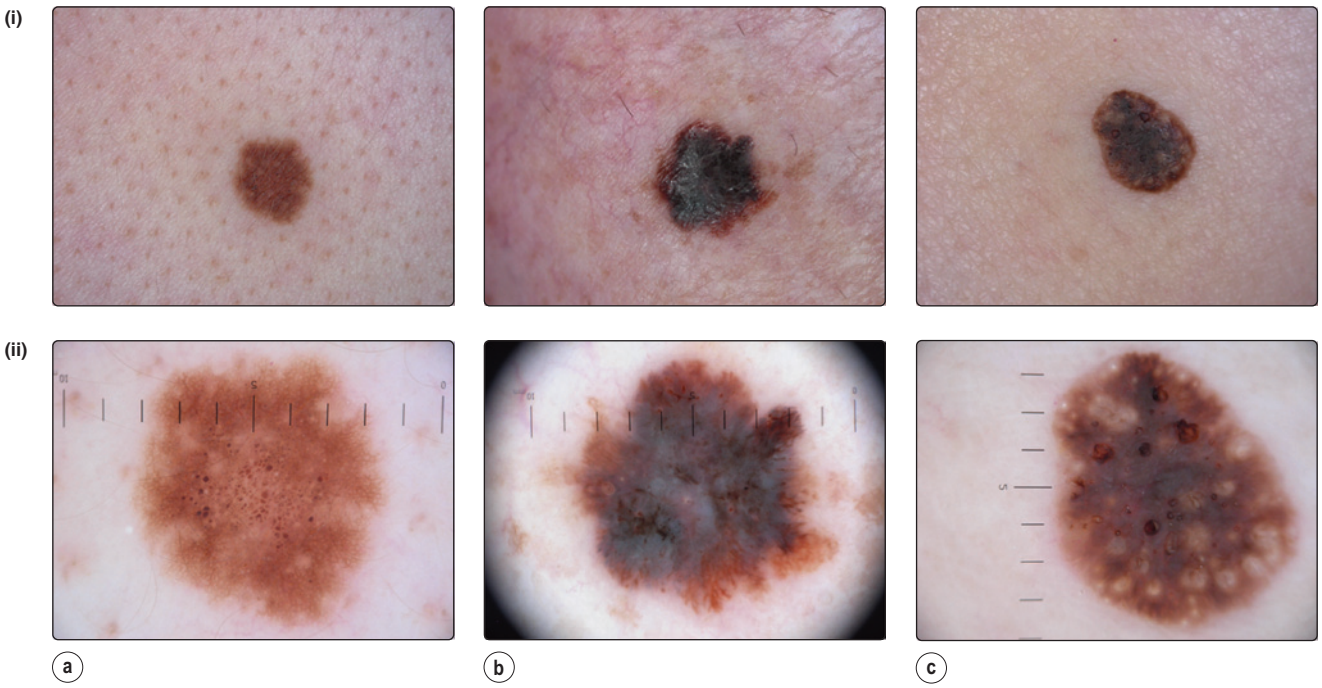


Fig. 10.2 Use of the dermoscope in (a) a benign melanocytic naevus, (b) a malignant melanoma, (c) a seborrhoeic wart. Comparison of the macroscopic (i) and dermoscopic (ii) appearances in each case.

Dermoscopy, the taking of samples for fungal culture and microscopy, the identification of scabies, the use of Wood's light, the ability to perform Doppler studies and the demonstration of dermographism are all practical procedures essential in general dermatology. These and the practical treatment procedures such as intralesional injection and skin paring are included in the curriculum for Specialty Training in Dermatology of the Joint Royal Colleges of Physicians Training Board (access via http://www.jrcptb.org.uk/). There are several online facilities to help the medical student or trainee develop skills in these areas. Some useful sites are listed below.

A hand lens helps when looking at small lesions such as nits on hair shafts (Fig. 10.1) or scabetic burrows, but dermoscopy gives added information, especially for pigmented lesions (Fig. e10.1). Dermoscopy employs a ×10 magnification illuminated lens system, which can visualize a lesion after the application of a drop of oil or water between the skin and the applied lens. Detailed visualization of the epidermal structures is possible, particularly the pigment network (Fig. 10.2). Analysis takes account of:

The Dermoscopy.org website takes the novice through the theory and practicalities of the topic (access via http://www.dermoscopy.org/). Dr Ian McColl of the Australian Institute of Dermatology has made a number of useful videos entitled 'Dermoscopy Made Simple' (access via https://www.youtube.com/).

Fungal culture and microscopy

The practicalities of how to take skin scrapings for fungal culture are described on the DermNet website (see 'Laboratory tests for fungal infection', access via http://www.dermnetnz.org/). An acceptable video can be found under 'skin scraping for fungal infection' on the YouTube site (access via https://www.youtube.com/).

Identification of scabies

The LA County website takes healthcare professionals through the procedure for identifying the acarus by skin scraping (search under 'scabies', access via http://publichealth.lacounty.gov/).

Fig. e10.1 Dermoscope.

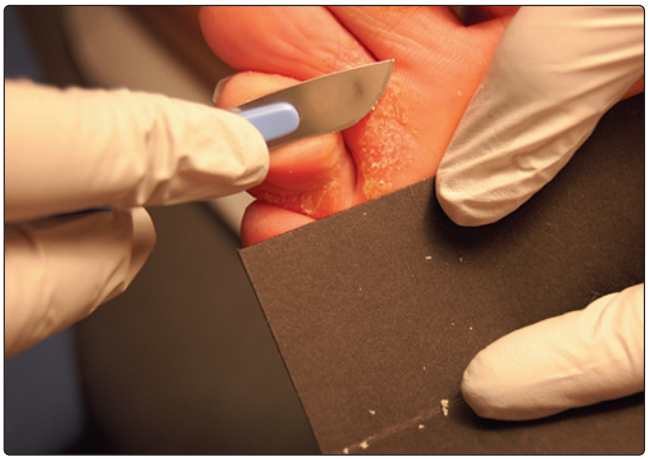


Fig. 10.3 Take a scraping from the edge of an area of suspected fungal infection by using a disposable scalpel blade.

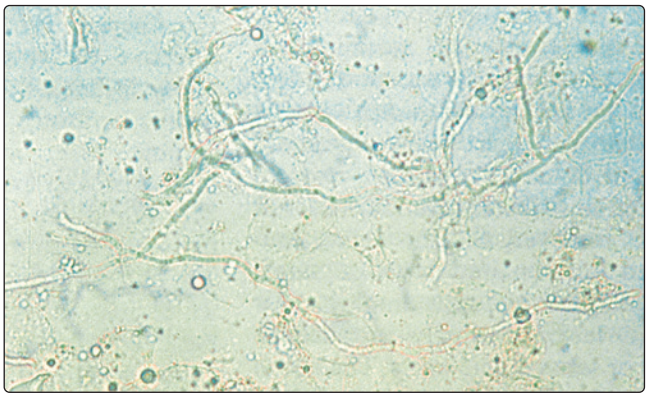


Fig. 10.4 Microscopy of skin scrapings showing fungal hyphae.

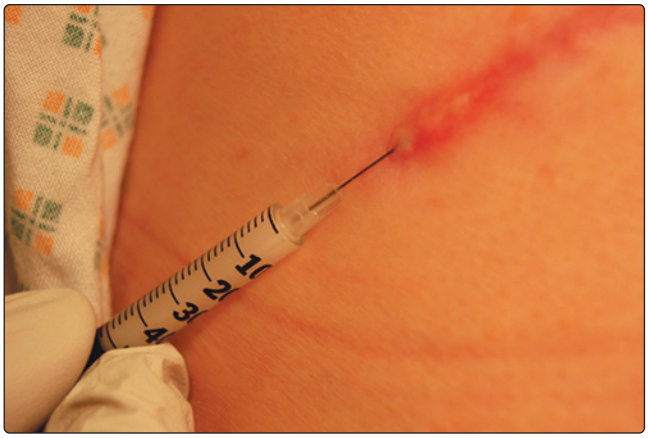


Fig. 10.5 Intralesional injection of steroid into a hypertrophic scar.

- diagnosing bacterial infections such as erythrasma (p. 52)
- diagnosing tinea capitis due to *Microspora* species.

Dermographism

Stroking the skin in patients with symptomatic dermographism will induce whealing (p. 80). Cold-induced urticaria can be provoked by the application of an ice cube to the skin. Rubbing a lesion of urticaria pigmentosa will produce a localized wheal (p. 120).

Doppler studies

The measurement of the ankle/brachial blood pressure index (ABPI) is essential in the management of patients with leg ulcers (p. 76). The ABPI must be >0.8 for compression therapy.

Therapeutic procedures

Dermatologists use some non-surgical techniques in their clinical work. Surgical methods and cryotherapy are dealt with elsewhere (pp. 114–119).

Intralesional steroid injection

The injection of steroid into the skin is useful in the management of several diseases, including:

- Alopecia areata
- Keloid or hypertrophic scars
- Acne cysts
- Granuloma annulare
- Hypertrophic lichen planus
- Prurigo nodularis
- Nail psoriasis.

Triamcinolone acetonide (10 mg/mL) is normally used in an insulin syringe, which has an integral needle. An injection of 0.1–1.0 mL of the solution is given into the mid or deep dermis (Fig. 10.5). The main side-effects are skin atrophy, hypopigmentation and telangiectasia. Occasionally, injection of other substances into the skin is used, e.g. bleomycin for viral warts (p. 55).

Paring of skin

The paring down of hyperkeratotic areas on the hands or feet using a disposable scalpel often helps in:

- **diagnosis**, as it can reveal the underlying lesion, e.g. the punctate thrombosed capillaries of a viral wart or a small haematoma within the epidermis (such as that produced by the friction of shoes on the heel)
- **therapy**, e.g. for callosities under the metatarsals, by reducing the pressure that results from the callus.

On the feet, callosities often develop as a result of the interaction of external forces and an abnormal anatomy of the foot. The advice of a chiropodist or podiatrist will usually be helpful.

Use of caustics

Xanthelasma around the eyes (p. 88) can be treated by the careful application of the caustic trichloroacetic acid (30–50%) solution on an almost dry cotton applicator. Great care is needed to protect the eyes. The treatment should be carried out only by those experienced in the procedure. The xanthelasma turns white with 'frosting' within seconds of application of the acid, and subsequently the treated skin peels off over a period of days.

Procedures in the skin clinic

- **Dermoscopy** is useful in deciding whether or not a pigmented lesion might be a malignant melanoma.
- **Skin scrapings for mycology** should be taken from the edge of a suspect area using a disposable scalpel blade onto a piece of black paper.
- **Wood's light** can show the extent of vitiligo or diagnose erythrasma or tinea capitis.
- **Intralesional triamcinolone** is a useful treatment for alopecia areata, keloid, acne cysts and other diseases. Skin atrophy is a potential side-effect.
- **Paring of skin** can reveal the underlying condition, e.g. a viral wart, or be a treatment for callosity.
- **Application of caustic:** trichloroacetic acid is used with care in the treatment of xanthelasma.

Use of Wood's light

More details on the use of Wood's light can be found at the Skinsight website (access via http://www.skinsight.com/).

Demonstration of dermographism

Some sufferers have made their own videos of the condition and illustrate how to demonstrate the disease (access via https://www.youtube.com/).

The practicalities of performing an arterial Doppler examination are demonstrated on a video (access via https://www.youtube.com/).

Dr J Levitt has produced a video that shows how to do an intralesional injection of steroid (access via https://www.youtube.com/). Dr MH Tirgan shows how to inject a keloid with steroid (access via https://www.youtube.com/).

A video by Dr V Yadav shows how to pare the skin of a callus (search under 'paring of corn' access via https://www.youtube.com/).

The use of trichloroacetic acid for xanthelasma is demonstrated by Dr M Gonzalez in a video (search under 'xanthelasmata treatment on embarrassing bodies'; access via https://www.youtube.com/).

Further reading – textbooks

Johr, R.H., Argenziano, G., 2011. Dermoscopy: The Essentials, second ed. WB Saunders, Philadelphia, PA.

11 Basics of medical therapy

The treatment of skin disease includes: topical, systemic, intralesional, radiation and surgical modalities. Specific treatments are detailed below. First is an overview of dermatological therapies.

Topical therapy

Topical treatment has the advantage of direct delivery and reduced systemic toxicity. It consists of a *vehicle* or base, which often contains an active ingredient (Table 11.1).

Vehicles are defined as follows:

- **Lotion.** A liquid vehicle, often aqueous or alcohol-based, which may contain a salt in solution. A *shake lotion* contains an insoluble powder (e.g. calamine lotion).
- **Cream.** A semisolid emulsion of oil-in-water; contains an emulsifier for stability and a preservative to prevent overgrowth of microorganisms.
- **Gel.** A transparent semisolid, non-greasy aqueous emulsion.
- **Ointment.** A semisolid grease or oil, containing little or no water but sometimes with added powder. No preservative is usually needed. The active ingredient is suspended rather than dissolved.
- **Paste.** An ointment base with a high proportion of powder (starch or zinc oxide) producing a stiff consistency.

Table 11.1 **An overview of topical medicaments**

Drug	Indications	Pharmacology
Corticosteroids	Eczemas, psoriasis, lichen planus, discoid lupus erythematosus, sunburn, pityriasis rosea, mycosis fungoides, photodermatoses, lichen sclerosus	Mode of action is through vasoconstrictive, antiinflammatory and antiproliferative effects; medication is available in different strengths; side-effects need to be considered
Antiseptics	Skin sepsis, leg ulcers, infected eczema	Chlorhexidine, benzalkonium chloride, silver nitrate and potassium permanganate are used
Antibiotics	Acne, rosacea, folliculitis, impetigo, infected eczema	Chlortetracycline, neomycin, bacitracin, polymixin B, retapamulin, fusidic acid and mupirocin; resistance and sensitization are problems Metronidazole is used for rosacea
Antifungals	Fungal infections of the skin, *Candida albicans* infections	Nystatin, clotrimazole, miconazole, econazole, terbinafine, ketoconazole and amorolfine
Antiviral agents	Herpes simplex, herpes zoster	Aciclovir, penciclovir
Parasiticidals	Scabies, lice	Benzyl benzoate, permethrin and malathion for scabies; malathion and permethrin for lice – applied as a lotion or shampoo
Coal tar	Psoriasis, eczema	Presumed antiinflammatory and antiproliferative effects; available as creams, shampoos and in paste bandages
Dithranol	Psoriasis	Antiproliferative effects; available as creams, pastes and ointments
Vitamin D analogues	Psoriasis	Calcitriol, calcipotriol and tacalcitol inhibit keratinocyte proliferation and promote differentiation
Keratolytics	Acne, scaly eczemas	Salicylic acid, benzoyl peroxide and tretinoin
Retinoids	Acne, psoriasis	Isotretinoin (acne), tazarotene (psoriasis)
Topical immunomodulators (calcineurin inhibitors)	Atopic eczema (and off-licence use in other diseases)	Tacrolimus and pimecrolimus

Therapeutic properties of the vehicle

Lotions evaporate and cool the skin and are useful for inflamed or exudative conditions, e.g. for wet wraps (p. 38). The high water content of a cream means that it mostly evaporates; it is also non-greasy and easy to apply or remove. Ointments are best for dry skin conditions such as eczema. They rehydrate and occlude, but being greasy are difficult to wash off and are less acceptable to patients than creams. Pastes are ideal for applying to well-defined surfaces, such as psoriatic plaques, but are also hard to remove.

Quantities required

One application to the whole body requires 15–20 g of ointment. The adult face or neck requires 1 g, trunk (each side) 3 g, arm 0.5 g, hand 0.5 g, leg 3 g and foot 1 g. A useful guide for patients is the '*fingertip unit*' (FTU) – the amount of cream or ointment that can be applied to the terminal phalanx of the index finger (Fig. 11.1). One FTU equals 0.5 g. The weekly amount required for the twice-daily use of an emollient in an adult is 250 g. Doctors often underestimate the quantities needed.

The safe maximum amount varies with the strength of the steroid, the age of the patient and the length of treatment. For 1% hydrocortisone, adults can use 150–200 g/week, but children can use only 60 g and babies as little as 20 g. Creams/ointments are applied twice daily, except for mometasone, fluticasone and tacalcitol, which are used once daily.

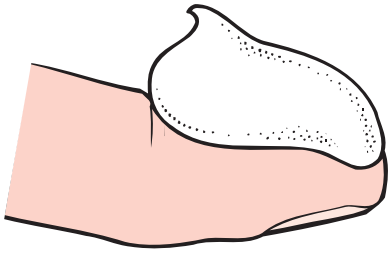


Fig. 11.1 The fingertip unit (FTU) = 0.5 g.

Pharmacokinetics

The ability of a drug to penetrate the epidermis depends on several factors. These include:

- the drug's molecular size and structure and its lipid/water solubility
- the vehicle used and whether application is occluded
- the site on the body – absorption is greatest through the eyelid and genitalia
- whether or not the skin is diseased.

Emollients

Emollients help dry skin conditions such as eczema and ichthyosis by re-establishing the surface lipid layer and enhancing rehydration of the epidermis. Common emollients include emulsifying ointment, Aveeno, Diprobase, Doublebase, E45, Epaderm, Hydromol, Ultrabase and Unguentum M creams. Sometimes emollients contain urea (Aquadrate, Eucerin Intensive) or antimicrobials (Dermol, Eczmol). Oils added to bath water can also help, e.g. Aveeno, Balneum, Cetraben, Dermolo, Diprobath, Doublebase, E45, Hydromol and Oilatum.

There are numerous websites that expand on topical treatments, under a variety of guises. The Merck Manual is especially comprehensive (search under 'dermatologic disorders', access via http://www.merckmanuals.com). Other useful sources include the WebMD and the DermNet websites (search under 'skin problems and treatment' or under specific conditions; access via http://www.webmd.com/ and http://dermnetnz.org/).

The British National Formulary (BNF) give details of the quantities that should reasonably be dispensed for specific parts of the body for twice daily application over a period of 1 week. Their advice, which one might regard as rather conservative, is as follows:

Area of body	Creams and ointments	Lotions
Face	15–30 g	100 mL
Both hands	25–50 g	200 mL
Scalp	50–100 g	200 mL
Both arms or both legs	100–200 g	200 mL
Trunk	400 g	500 mL
Groins and genitalia	15–25 g	100 mL

The Medicines Complete website can be searched for further details (search under 'suitable quantities for prescribing topical therapies', access via https://www.medicinescomplete.com/).

In the BNF there is specification of the suggested quantities of topical steroids that might be prescribed for once daily application for a 2-week course. These are conservative estimates, perhaps based on the all too common fear of the over-prescribing of steroids, and should be seen as the lowest amounts that might be used. The BNF recommendations are as follows:

Area of body	Steroid cream or ointment
Face and neck	15–30 g
Both hands	15–30 g
Scalp	15–30 g
Both arms	30–60 g
Both legs	100 g
Trunk	100 g
Groins and genitalia	15–30 g

The University of Hertfordshire provides expert detail on this topic (search under 'pharmacokinetics of topical products, 2012', access via http://researchprofiles.herts.ac.uk).

NHS Choices and the British Dermatological Nursing Group provide useful information on the use of emollients (search 'emollients', access via http://www.nhs.uk/ and search 'best practice emollients', access via http://www.bdng.org.uk/). A video on the use of emollients in eczema has been developed by the University of Glasgow, search under 'skin deep, emollient therapy', access via https://www.youtube.com/).

Dressings and hospital admission

Many departments have treatment centres where daily dressings and ultraviolet (UV) treatments are given. If outpatient management is unsuccessful, hospital admission may be needed. Dressings, for either the outpatient or the inpatient, consist of stockinette gauze applied to the trunk or limbs after the ointments have been put on. These must be changed once or twice a day. Leg ulcer dressings may be changed less frequently, depending on the type of application used.

Bandages impregnated with tar are sometimes helpful for leg ulcers and eczema. Many types of paraffin gauze, hydrocolloid and alginate dressing are now available for leg ulcers (p. 76).

Topical steroids

A summary of the indications for topical treatment with corticosteroids is given in Table 11.1. The relative potencies of the more commonly prescribed preparations are shown in Table 11.2.

Side-effects of topical steroid therapy

The use of topical steroids carries the potential for harmful side-effects. These include:

- Atrophy of the skin – thinning, erythema, telangiectasia, purpura and striae (Fig. e11.2)
- Induction of acne or perioral dermatitis, and exacerbation of rosacea
- Atypical fungal infection (tinea incognito); bacterial or viral infections may be potentiated
- Allergic contact dermatitis, resulting from a component of the preparation or the steroid itself
- Systemic absorption – suppression of the pituitary–adrenal axis, cushingoid appearance, growth retardation
- Tachyphylaxis – reduced responsiveness to the steroid after prolonged use.

Table 11.2 Relative potencies of topical steroids

Potency	Example (generic name)	Proprietary name (UK/USA)
Mild	Hydrocortisone 1% and 2.5%	Efcortelan, Mildison (U-Cort USA)
Moderately potent	Alclometasone dipropionate 0.05% Clobetasone butyrate 0.05% Fluocortolone caproate/pivalate 0.25% Fludroxycortide 0.0125%	Modrasone (Aclovate USA) Eumovate (UK and USA) Ultralanum Plain (UK) Haelan (UK), Cordran (USA)
Potent	Betamethasone valerate 0.1% Betamethasone dipropionate 0.05% Fluocinolone acetonide 0.025% Fluocinonide 0.05% Fluticasone propionate 0.05% Hydrocortisone butyrate 0.1% Mometasone furoate 0.1%	Betnovate (Valisone USA) Diprosone (UK and USA) Synalar (UK and USA) Metosyn (Lidex USA) Cutivate (UK and USA) Locoid (UK and USA) Elocon (UK and USA)
Very potent	Clobetasol propionate 0.05% Diflucortolone valerate 0.3% Halobetasol propionate 0.05%	Dermovate (Temovate USA) Nerisone Forte (UK and Canada) Ultravate (USA)

Table 11.3 An overview of systemic therapy

Group	Drug	Indications
Corticosteroids	Prednisolone usually	Bullous disorders, connective tissue disease, vasculitis
Cytotoxics	Methotrexate Hydroxycarbamide	Psoriasis, sarcoidosis, eczema Psoriasis
Biologics	Etanercept, infliximab, adalimumab, ustekinumab	Psoriasis unresponsive to other systemic agents, off-licence use in other diseases (p. 33) ℞
Immunosuppressants	Ciclosporin Gold Azathioprine, mycophenolate mofetil	Psoriasis, atopic eczema, pyoderma gangrenosum Bullous disorders, lupus erythematosus Bullous disorders, chronic actinic dermatitis, atopic eczema
Retinoids	Acitretin Isotretinoin Alitretinoin	Psoriasis, other keratinization disorders Acne Hand dermatitis ℞
Antifungals	Griseofulvin, terbinafine Ketoconazole Itraconazole, fluconazole	Fungal infection Fungal infection (*Candida albicans* too) Fungal infection, candidiasis
Antibiotics	Various	Skin sepsis, acne, rosacea
Antivirals	Aciclovir, valaciclovir Famciclovir	Herpes simplex, herpes zoster Herpes zoster, genital herpes simplex
Antihistamines	H1 blockers	Urticaria, eczema
Antiandrogens	Cyproterone acetate	Acne (females only)
Antimalarials	Hydroxychloroquine	Lupus erythematosus, porphyria cutanea tarda
Antileprotic	Dapsone	Dermatitis herpetiformis, leprosy, vasculitis

Systemic therapy

Systemic treatments are used when topical treatment is ineffective, for serious skin diseases and for infections. Details are given in Table 11.3.

Other treatments

Corticosteroids are sometimes injected directly into lesions (e.g. to treat keloids). Certain disorders respond to phototherapy (p. 112). Iontophoresis is a treatment for excess sweating of the palms, in which a direct electric current is passed into skin in contact with tap water.

In the past, X-irradiation was used to treat psoriasis, acne, tinea capitis, tuberculosis of the skin and hand eczema. There are now very few indications for X-ray treatment of non-malignant disease, although irradiation is of great value in several types of skin tumour.

Cryotherapy, in which liquid nitrogen is applied to the skin, is extensively used in dermatology (p. 115). It is mainly employed for the treatment of benign or premalignant skin tumours.

Basics of medical therapy

- Correct diagnosis is essential to ensure appropriate treatment.
- When using topical steroids:
  - use the lowest potency that is effective
  - look out for side-effects, especially atrophy of the skin
  - emollients can help reduce the amount of topical steroid required.
- Explain the treatment to the patient and preferably give a written handout; this aids compliance. The fingertip unit is a convenient way to indicate the amount of cream the patient should apply.
- Use the simplest treatment possible; patients easily get mixed up if they have several different topical preparations to apply to different parts of the body.
- Prescribe adequate amounts. Patients are often given too small quantities of their creams, 'run out' and return to the clinic with no improvement because the treatment has been inadequate.

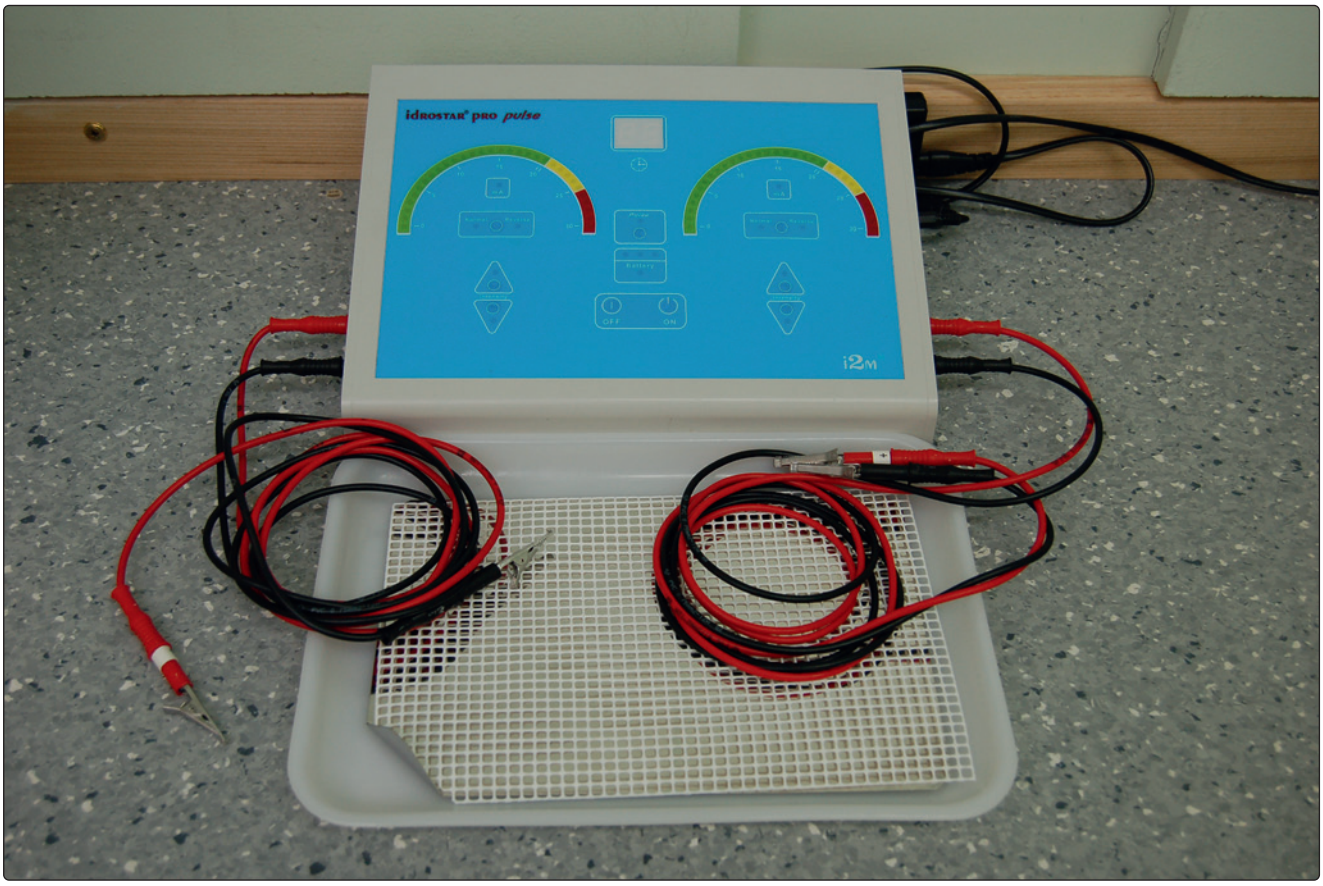


Fig. e11.1 An iontophoresis machine.

Detail of the types and appropriateness of dressings, especially for leg ulcers, can be found at the Worldwide Dressings website (search under 'moisture related skin damage', access via http://www.worldwidewounds.com).

NHS Choice gives a good overview on the use of topical corticosteroids, including details of side-effects (access via http://www.nhs.uk/).

Corticosteroids are sometimes injected directly into lesions (e.g. to treat keloids). Certain disorders respond to phototherapy (p. 112). Iontophoresis is a treatment for excess sweating of the palms, in which a direct electric current is passed into skin in contact with tap water (Fig e11.1).

- Atrophy of the skin – thinning, erythema, telangiectasia, purpura and striae (Fig. e11.2)

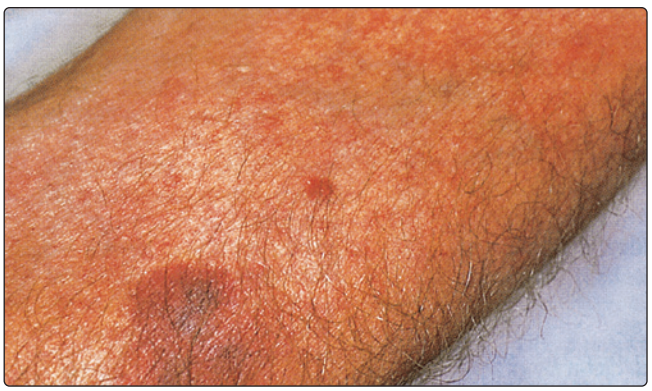


Fig. e11.2 Skin atrophy with purpura due to excessive topical use of a potent steroid.

Further reading – textbooks

Lebwohl, M.G., Heymann, W.R., Berth-Jones, J., et al. (Eds.), 2013. Treatment of Skin Disease, fourth ed. WB Saunders, Philadelphia, PA.

Wakelin, S.H., Maibach, H.I., Archer, C.B., 2015. Handbook of Systemic Drug Treatment in Dermatology, second ed. CRC Press, Boca Raton, FL.

Williams, H., Bigby, M., Diepgen, T., et al. (Eds.), 2008. Evidence Based Dermatology, third ed. Blackwell, Oxford.

12 Epidemiology of skin disease

Skin disease is very common. About 10% of a GP's workload and 6% of hospital outpatient referrals can be accounted for by skin problems. Skin disease is also economically significant; it is a major occupational cause of loss of time from work and the third most common industrial disease (p. 132).

In any discussion of epidemiology, it is important first to define the terms used:

- *Prevalence* refers to the proportion of a defined population affected by a disease at any given time.
- *Incidence* is defined as the proportion of a population experiencing the disorder within a stated period of time (usually 1 year).

The type, prevalence and incidence of skin disease all depend on social, economic, geographical, racial, cultural and age-related factors.

Skin disease in the general population

Reliable population statistics are difficult to obtain, but it appears that, in Europe, the prevalence of skin disease needing some sort of medical care is about 20%. Eczema, acne and infective disorders (including warts) are the commonest complaints (Fig. 12.1). Only a minority seek medical advice.

Skin disease in community and specialized clinics

The precise proportion of skin disorders seen in a community setting (Fig. 12.2) will vary with the age structure of the population served, the amount and type of industry in the area and socioeconomic factors. Demographic studies may reveal a trend; e.g. for unknown reasons, atopic eczema has become more common over the last 40 years.

Patients seen in a specialist dermatology clinic are a selected population (Fig. 12.3). In some countries, e.g. the UK, a GP will have referred them; in other places, self-referral may depend on the availability of medical insurance. Referral patterns vary between different regions, depending on local facilities, interests and customs. In Europe, within a year, just over 1% of the population is referred for a dermatological opinion. In the early 2010s, one-quarter of all new referrals required a surgical procedure.

Socioeconomic factors

Improvements in the standard of living resulting from the 19th-century industrialization of Europe were accompanied by a fall in the incidences of most infectious diseases and a decline in the infant mortality rate. Better nutrition, improved living conditions and the introduction of hygienic measures are thought to have been important. Most forms of infectious disease, including those of the skin, are now more common in the developing world than in Westernized countries, and it would seem that the poorer standards of living are a cause of this.

However, industrialization brings its own problems. Occupational dermatitis is quite common in industrialized countries, and mild cases are often not reported. Increased sophistication in Western countries also means that patients now want something done about disorders or minor imperfections that would not have bothered past generations.

Changes in social fashion have also brought about changes in skin disease. For example, the habit of sunbathing, which became popular in the 1970s, seems to have resulted in an increase in the incidence of malignant melanoma from the 1980s to the present.

The media have also had an effect: the numerous articles and programmes on the potential problems associated with a change in pigmented naevi have produced a flood of referrals of worried patients seeking reassurance about their lesions. However, it is still true that many people with minor skin problems do not consult a doctor.

Geographical factors

Humid conditions found in hot countries predispose to fungal and bacterial

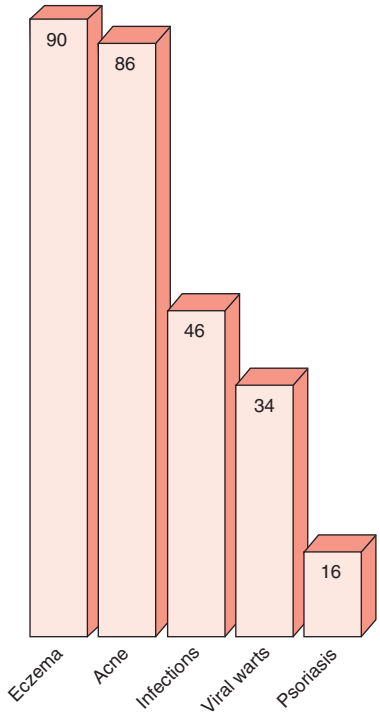


Fig. 12.1 Prevalence per 1000 population for skin disease of any severity.

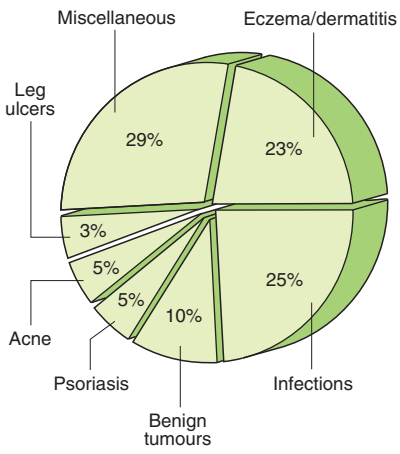


Fig. 12.2 Breakdown of skin diseases seen in general practice (% of total).

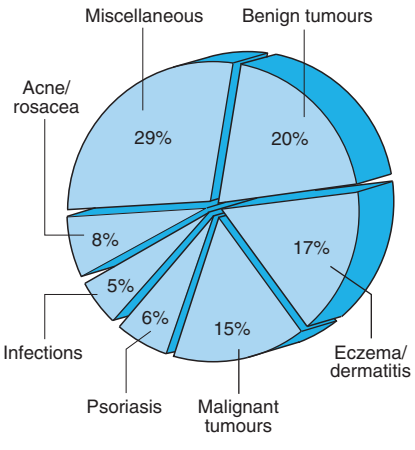


Fig. 12.3 Breakdown of skin diseases seen in a hospital dermatology clinic (% of total).

The incidence of skin diseases can be difficult to estimate in the general population. One of the first investigations attempted was a 1976 community-based study from Lambeth in London, England, which showed a prevalence of eczema of 6% (see: JN Rea, ML Newhouse, T Halil 1976. Skin disease in Lambest. Br J Prev Med 30:107–114; accessible via http://www.ncbi.nlm.nih.gov/).

In a more recent article from the Mayo Clinic in Rochester, Minnesota, USA, the authors have reviewed the literature and produced figures for the incidence of most major skin diseases for the state of Minnesota over the last 40 years (see: LK Anderson, MD Davis 2013. The epidemiology of skin and skin-related diseases. Mayo Clinic Proceedings 88:1462–1467; accessible via http://www.ncbi.nlm.nih.gov/).

The WHO provide an excellent guide, downloadable as a pdf, on the epidemiology and management of skin disease in childhood in developing countries. This guide outlines the literature and supplies management algorithms (WHO. The Epidemiology and Management of Common Skin Diseases in Children in Developing Countries; accessible via http://www.who.int/).

infections, and to other conditions such as 'prickly heat' (miliaria: an itchy eruption due to blocked sweat ducts). Ultraviolet radiation in sunny climes will result in actinic damage and malignant change in the skin of non-pigmented migrants to the area.

Fig. 12.4 shows a comparison between some common complaints in different geographical locations. The rates for bacterial and fungal infections show variation, and skin cancers are more common in Australia. However, the figures for eczema/dermatitis are remarkably constant.

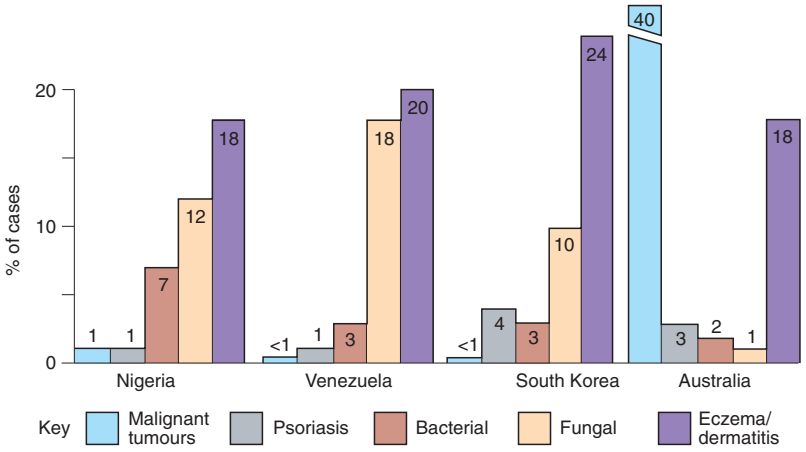


Fig. 12.4 Geographical variations in hospital attendances (%) with some common dermatological disorders.

Racial and cultural factors

Quite apart from the obvious differences in pigmentation, the skin structure varies between the different races (p. 130). For example, hair is often spiral in black Africans but straight in Mongoloids. In Caucasians, hair is more variable and may be straight, wavy or helical. Skin tumours and actinic damage are seen more in Caucasians than in black Africans, with Mongoloids showing an intermediate incidence. Keloids and hair problems, such as pseudofolliculitis (p. 131), are more common in black Africans, whereas Mongoloid skin has a tendency to become lichenified and acne may be less frequent. Vitiligo appears to have a similar incidence in all races, but is more conspicuous and may have a greater psychological impact in those with a dark skin.

Cultural factors may bring problems. For example, tight braiding of the hair, practised by some black Africans, may result in alopecia, whereas the use of certain traditional oils or cosmetics can produce dermatitis or a change in pigmentation.

Age and sex prevalence of dermatoses

Different disorders are associated with different times of life (Table 12.1). Some disorders occur throughout life but are more common at certain ages, whereas others are almost exclusively encountered in defined age groups. For example, atopic eczema is most common in infants, acne is mainly seen in adolescents and psoriasis has its peak onset in the second and third decades of life. Certain disorders tend to appear in middle age, e.g. pemphigus and malignant melanoma. In old age, degenerative and malignant skin conditions are often found. Thus, the age structure of the population will influence the type of dermatology practised.

Some conditions are more common to a specific gender (Table 12.2).

Table 12.1 Age-related onset of selected skin disorders

Age	Disorder
Childhood	Port-wine stain and strawberry naevi, ichthyosis, erythropoietic protoporphyria, epidermolysis bullosa, atopic eczema, infantile seborrhoeic dermatitis, urticaria pigmentosa, viral exanthems, viral warts, molluscum contagiosum, impetigo
Adolescence	Melanocytic naevi, acne, psoriasis (notably guttate), seborrhoeic dermatitis, vitiligo, pityriasis rosea
Early adulthood	Psoriasis, seborrhoeic dermatitis, lichen planus, dermatitis herpetiformis, lupus erythematosus, vitiligo, tinea versicolor
Middle age	Porphyria cutanea tarda, lichen planus, rosacea, pemphigus vulgaris, venous ulceration, malignant melanoma, basal cell carcinoma, mycosis fungoides
Old age	Asteatotic eczema, generalized pruritus, bullous pemphigoid, venous and arterial ulcers, seborrhoeic warts, solar keratosis, solar elastosis, Campbell-de-Morgan spots, basal cell carcinoma, squamous cell carcinoma, herpes zoster

Table 12.2 Skin disorders with a male or female preponderance

Sex	Disorder
Female	Palmoplantar pustulosis, lichen sclerosus, lupus erythematosus, systemic sclerosis, morphoea, rosacea, dermatitis artefacta, venous ulceration, in situ squamous cell carcinoma, malignant melanoma
Male	Seborrhoeic dermatitis, dermatitis herpetiformis, porphyria cutanea tarda, polyarteritis nodosa, pruritus ani, tinea pedis and cruris, mycosis fungoides, squamous cell carcinoma, actinic keratosis

Epidemiology

- The commonest skin diseases in the general community are eczema, acne and infections, including viral warts.
- About 20% of the general population have some sort of skin disorder requiring medical attention.
- Skin disease accounts for more than 10% of all consultations in general practice.
- Better living conditions reduce skin infection, but excess sun on a white skin predisposes to skin cancer.

Table e12.1 **The incidence of basal and squamous cell carcinomas reduces with increasing latitude in a Caucasian population**

Geographic area (year of report)	Latitude	BCC male/female	SCC male/female	Total (NMSC) male/female
Townsville, Australia (1998)	19°S	2058/1195	1332/755	3390/1950
Nambour, Australia (1996)	27°S	2074/1579	1035/472	3109/2051
Nambour, Australia (2006)	27°S	1813/1269	–	–
Arizona (2001)	31°N	936/497	270/112	1206/609
New Hampshire (1999)	42°N	310/165	97/32	407/197
Rochester, MN (1997/1990)	43°N	175/124	155/71	330/195
Vaud, Switzerland (2001)	46°N	75/66	29/17	104/83
British Columbia, Canada (1990)	49°N	120/92	31/7	151/99
West Glamorgan, Wales (2000)	51°N	128/105	25/9	153/114
Netherlands (1991)	52°N	46/32	11/3	57/35
Hull, England (1994)	53°N	116/103	29/21	145/124
Finland (1999)	62°N	49/45	7/4	56/49

From Bolognia JL, Jorizzo JL, Schaffer JV, Dermatology, 3rd edn. Saunders, with permission.

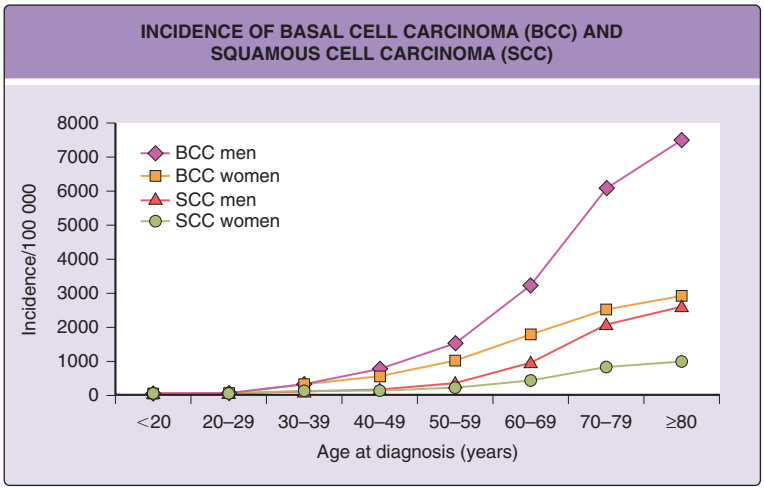


Fig. e12.1 The incidence of basal and squamous cell carcinomas by age and sex. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd edn. Saunders, with permission.)*

An increase in latitude as one moves away from the equator (i.e. a proxy for reducing sun exposure) is associated with a decrease in the incidence of non-melanoma skin cancer (Table e12.1), as one might expect.

The commonest group of skin diseases influenced by race is skin cancer, and the Centers for Disease Control and Prevention in the USA has provided excellent graphs to demonstrate this (search as 'skin cancer rates by race and ethnicity', access via http://www.cdc.gov).

Other skin diseases may show different prevalences in different racial groups. One example is lupus erythematosus (search under 'who gets lupus', access via http://www.lupusny.org/).

Several researchers have examined the question of the difference in prevalences of common skin diseases in the different age groups (abstracts of papers can be viewed on the PubMed website: search under the prevalence of skin disease in 'childhood', 'adolescence' or 'old age'; access via http://www.ncbi.nlm.nih.gov/).

One example where both age and gender have an effect on disease prevalence is basal and squamous cell skin cancer. The incidence of basal and squamous cell carcinomas increases with age and is different in men and women (Fig. e12.1).

Further reading – textbooks

Parish, L.C., Amer, M., Millikan, L.E., et al. (Eds.), 1994. Global Dermatology: Diagnosis and Management According to Geography, Climate and Culture. Springer-Verlag, New York.

Schofield, J., Grindlay, D., Williams, H.C., 2009. Skin Conditions in the UK: A Health Care Needs Assessment. University of Nottingham, UK.

13 Body image, the psyche and the skin

The stress of having skin disease

The potentially harsh psychological effects of chronic skin disease tend to be underestimated. Up to 30% of skin outpatients suffer 'psychological distress' from their condition. This is understandable in the teenager with acne, or in someone who has extensive psoriasis or eczema. In both, the individual's devalued body image may be out of proportion to the objective severity of his or her skin problem. Skin diseases can make patients into 'social lepers' who feel that their social lives are restricted because other people do not want to mix with them. Such psycho-cutaneous considerations are central in training curricula. The effects on 'quality of life' can be assessed by specific questionnaires, e.g. the Dermatology Life Quality Index (DLQI).

Patients sometimes feel that their disorder is either caused directly by, or exacerbated by, 'stress'. This is difficult to prove, as it is often impossible to differentiate reactive from aetiological states. Many dermatologists believe that psychological factors can, e.g. make eczema and psoriasis worse, but most would also agree that these are stressful conditions in their own right. However, it is accepted that there are a small number of conditions that are of psychogenic origin. Management with a liaison psychiatrist can be helpful.

Skin disorders of psychogenic origin

Dermatitis artefacta

Dermatitis artefacta (Fig. 13.1) should be suspected from the presence of lesions with bizarre shapes (often linear or angular and in accessible sites) that do not conform to natural disease. The lesions are often ulcerated or crusted and do not heal as expected, although they do heal if occluded. Blisters or bruises are also sometimes found.

The condition tends to occur in young women. Confrontation is not recommended, as this may lead to an angry denial. Management is aimed at excluding genuine disease, establishing a rapport with the patient and gently trying to investigate the presence of psychological stresses, e.g. in the home or work environment or in social or sexual relationships.

Delusions of body image

Patients may present with no objective skin disease but still complain of symptoms such as burning or redness of the face, or display a preoccupation with an imagined problem such as excessive facial hair. This condition, sometimes known as body dysmorphic disorder (previously dysmorphophobia), is usually seen in women, although it does occur in men, who may complain of a burning scrotum. Most of these patients are depressed, although some may show signs of schizophrenia. Psychiatric referral is needed for those with true delusions.

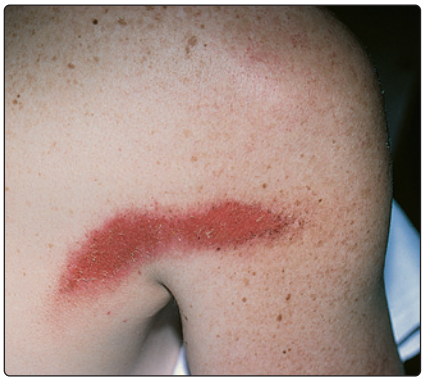


Fig. 13.1 Dermatitis artefacta: a linear lesion.

Delusions of infestation

Patients with this condition are convinced that their skin is infested with parasites, and they often bring collections of keratin and debris to support their contention. Self-induced excoriation of the skin may be seen. It mainly occurs in women over the age of 40 years. Most patients do not have an organic psychosis, but they are often obsessional and do have a monosymptomatic hypochondriacal psychosis. Treatment is difficult. It is necessary to exclude a true infestation. The antipsychotic drugs pimozide, risperidone or olanzapine may be helpful, but all have significant potential side-effects that require monitoring.

Trichotillomania

Rubbing, pulling and twisting the hair is not uncommon in children and results in thinning of scalp hair, which recovers spontaneously. When the condition occurs in adults, the hair may be cut using scissors or a razor, and the prognosis is not so good.

Pathological skin picking (neurogenic excoriations)

Accessible areas of the skin, particularly the forearms and back of the neck, are commonly involved in this condition, with excoriated lesions in a variety of stages of evolution from ulcers to healed scars (Fig. 13.2). The damage is inflicted as a result of an uncontrollable itch, but there is no primary lesion. Effective occlusion will allow healing. *Acné excoriée* is a variant seen in young women who squeeze and pick their acne lesions, resulting in artefactual erosions.

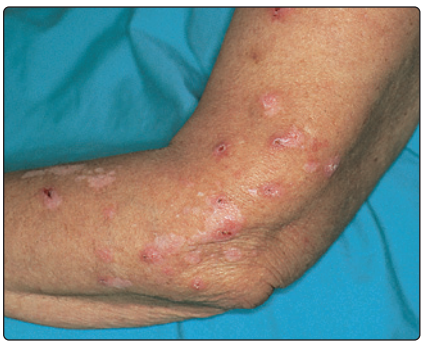


Fig. 13.2 Pathological skin picking on the arm. Some have healed to leave hypopigmented scars.

Body image, the psyche and the skin

- Psychological stress is commonly associated with skin disease, and the patient's psychological state should be routinely assessed. Quality of life questionnaires are available.
- Some skin disorders (e.g. eczema and psoriasis) may get worse at times of stress in certain patients. It may be helpful for the patient to recognize this.
- A small number of skin diseases are psychogenic in origin. A liaison psychiatrist may offer assistance.

Anxiety and depression, not surprisingly, may be precipitated by skin diseases of any type, and dermatologists need to be continually aware of this in the management of their patients. *Vitiligo*, affecting skin pigmentation (often on the face and hands) and *alopecia areata*, causing hair loss on the scalp, especially affect the way an individual appears to the outside world. Both can cause considerable social embarrassment and may result in discrimination. It is not surprising that anxiety, depression and adjustment disorder are found in a third or more of patients affected by these conditions.

The connexion between an individual having a skin disease and their psychological and social functioning is a good illustration of the so-called 'biopsychosocial' approach of looking at someone's health through more than just the medical aspects. It is a hot topic and several papers can be found on the subject (access via http://www.ncbi.nlm.nih.gov/). Most recent medical graduates will be trained in this anyway, and its importance is underlined by 'psycho-cutaneous medicine' being a specific progressive element in the UK training curriculum for Dermatology (access via http://www.gmc-uk.org/).

'*Psychodermatology*' is a relative recent subspecialty that deals with the management of patients in whom there are manifestations from the interaction of the psyche and the skin (see the article by M Jafferany 2007. Psychodermatology: a guide to understanding common psychocutaneous diseases. Prim Care Companion J Clin Psychiatry 9:203–215; access via http://www.ncbi.nlm.nih.gov/).

Dermatitis artefacta is a disease that can be difficult to diagnose as it is essentially a disorder of exclusion, though dermatologists frequently have an indication of the diagnosis from the overall initial presentation. Management often proves extremely difficult. For more information on dermatitis artefacts see the eMedicine and DermNet NZ websites (access via http://emedicine.medscape.com/ and http://www.dermnetnz.org/).

Delusions of infestation is one manifestation of the so-called Morgellons disease. Some people with this conditions complain of fibres coming out of their skin. More information is available at MedicineNet (access via http://www.medicinenet.com/). Patients with *delusions of body image (dysmorphophobia)* and *delusions of infestation* (sometimes called *delusions of parasitosis*) almost invariably have psychological or psychiatric problems and require collaborative management with a liaison psychiatrist.

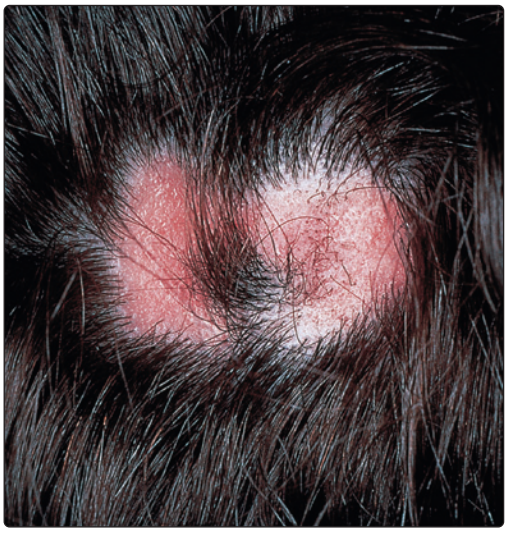


Fig. e13.1 Trichotillomania showing small areas of sparing and hairs of different length. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd edn. Saunders, with permission.)*

Psychologically, patients with *trichotillomania* may also show compulsive behaviour, but anxiety, depression and substance abuse and, in children, emotional neglect, also need to be considered (Fig. e13.1).

Compulsive skin picking (neurogenic excoriations) is regarded as a disorder with obsessive-compulsive and perfectionist traits. *Acné excoriée*, characterized by picking at acne lesions on the face, and usually seen in young women, can be associated with a number of psychological problems including depression and obsessive-compulsive behaviour, but also manifests in those with immature coping mechanisms and low self-esteem.

Further reading – textbooks

Bewley, A., Taylor, R.E., Reichenberg, J.S., Magid, M., 2014. Practical Psychodermatology. Wiley, Chichester.

2 Diseases

14 | **Psoriasis** – Epidemiology, pathophysiology and presentation

Definition

Psoriasis is a chronic, non-infectious, inflammatory dermatosis characterized by well-demarcated erythematous plaques topped by silvery scales (Fig. 14.1).

Epidemiology

Psoriasis affects 1.5–3% of the population in Europe and North America, but is less common in Africa, China and Japan. The sex incidence is equal. The condition may start at any age, even in the elderly. The two peaks of onset are the second to third and the sixth decades. It is unusual in children under 8 years old. An association with the metabolic syndrome is an important recent discovery.

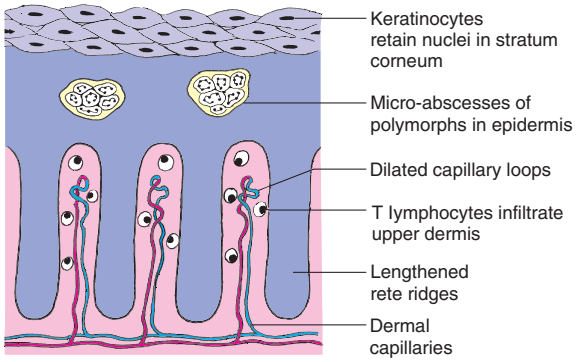


Fig. 14.1 Histopathology of psoriasis.

Aetiopathogenesis

Genetics

Inherited factors predispose to the development of psoriasis: genetic factors appear to be polygenic (p. 12). About 35% of patients show a family history, and identical twin studies show a concordance of 64%. There is a 14% probability that a child with one parent who has psoriasis will be affected, but this increases to 41% if both parents have psoriasis. There are strong correlations with the human leucocyte antigens (HLAs), e.g. HLA-Cw6. Environmental factors are thought to trigger the disease in susceptible individuals.

Epidermal kinetics and metabolism

Psoriatic lesions result from abnormal reactivity of skin T cells with alteration of the epidermal barrier and of inflammatory signalling. The number of cycling epidermal cells is increased seven-fold because of an increase in the basal and suprabasal proliferating cell compartment. The cell cycle time is not reduced. Growth factors, especially transforming growth factor-α, mediate these events. The upper dermal capillary plexus is expanded. At least nine possible chromosomal loci for genes linked to psoriasis have been found, e.g. *PSOR1* on chromosome 6p.

Precipitating factors

A number of precipitating factors are associated with the disorder:

- *Koebner phenomenon*. Trauma to the epidermis and dermis, such as a scratch or surgical scar (p. 19), can precipitate psoriasis in the damaged skin (Fig. 14.2).
- *Infection*. Typically, a streptococcal sore throat may precipitate guttate psoriasis.
- *Drugs*. Beta-blockers, lithium and antimalarials can make psoriasis worse or precipitate it.
- *Sunlight*. Exposure to sunlight can aggravate psoriasis (in about 6%), although it has a beneficial effect in the majority.
- *Psychological stress*. Stress can cause and exacerbate psoriasis.
- *Cigarettes and alcohol*. These seem to make psoriasis worse.

Pathology

The epidermis is thickened, with keratinocytes retaining their nuclei (see Fig. 14.1). There is no granular layer, and keratin builds up loosely at the horny layer. The rete ridges are elongated, and polymorphs infiltrate up into the stratum corneum where they form micro-abscesses. Capillaries are dilated in the papillary dermis. T lymphocytes infiltrate the earliest psoriatic lesions.

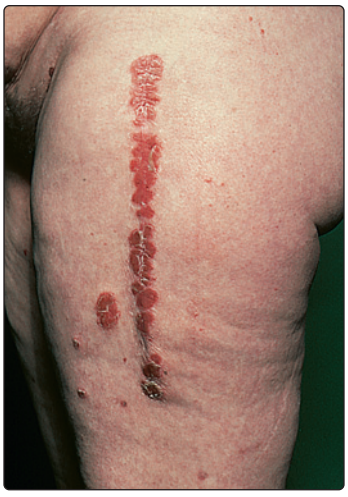


Fig. 14.2 The Koebner phenomenon. Psoriasis has developed in a surgical scar. *(From Buxton PK, Morris-Jones R 2009 ABC of Dermatology, 5th edn, Wiley-Blackwell, with permission.)*

Clinical presentation

Psoriasis varies in severity from the trivial to the life-threatening. Its appearance and behaviour also range widely from the readily recognizable chronic plaques on the elbows to the acute generalized pustular form. Psoriasis can be confused with other conditions (Table 14.1).

Presentation patterns of psoriasis include:

- plaque
- guttate
- flexural
- localized forms
- generalized pustular
- nail involvement
- erythroderma (p. 46)

Plaque

Well-defined, raised disc-shaped plaques (Fig. 14.3) involving the elbows, knees, scalp, hair margin or sacrum are the classic presentation (see also Fig. 8.1). The plaques are usually red and covered with waxy white scales, which, if detached, may leave bleeding points. Plaques vary in diameter from ≤2 cm to

Table 14.1 **Differential diagnosis of psoriasis**

Variant of psoriasis	Differential diagnosis
Plaque psoriasis	Psoriasiform drug eruption (due to beta-blockers) Hypertrophic lichen planus
Palmoplantar psoriasis	Hyperkeratotic eczema Reiter's disease
Scalp psoriasis	Seborrhoeic dermatitis
Guttate psoriasis	Pityriasis rosea
Flexural psoriasis	Candidiasis of the flexures
Nail psoriasis	Fungal infection of the nails

Some studies suggest psoriasis is slightly more common in women than in men. The prevalence in white-skinned North Americans is 2.5%, and is lower in people with darker skin types. See entry on Medscape website (search as 'psoriasis', access via http://emedicine.medscape.com/).

The causation of psoriasis has been extensively investigated in recent years and a better understanding has led to better treatments – see the section on Biologic drugs. Useful articles on the mediation of T cells and autoimmune factors in the pathophysiology of psoriasis can be accessed through the *Nature* publications website (access via http://www.nature.com).

Well-defined, raised disc-shaped plaques (Fig. 14.3 and Fig. e14.1) involving the elbows, knees, scalp, hair margin or sacrum are the classic presentation (see also Fig. 8.1). The plaques are usually red and covered with waxy white scales, which, if detached, may leave bleeding points. Plaques vary in diameter from ≤2 cm to several centimetres, and are sometimes pruritic.

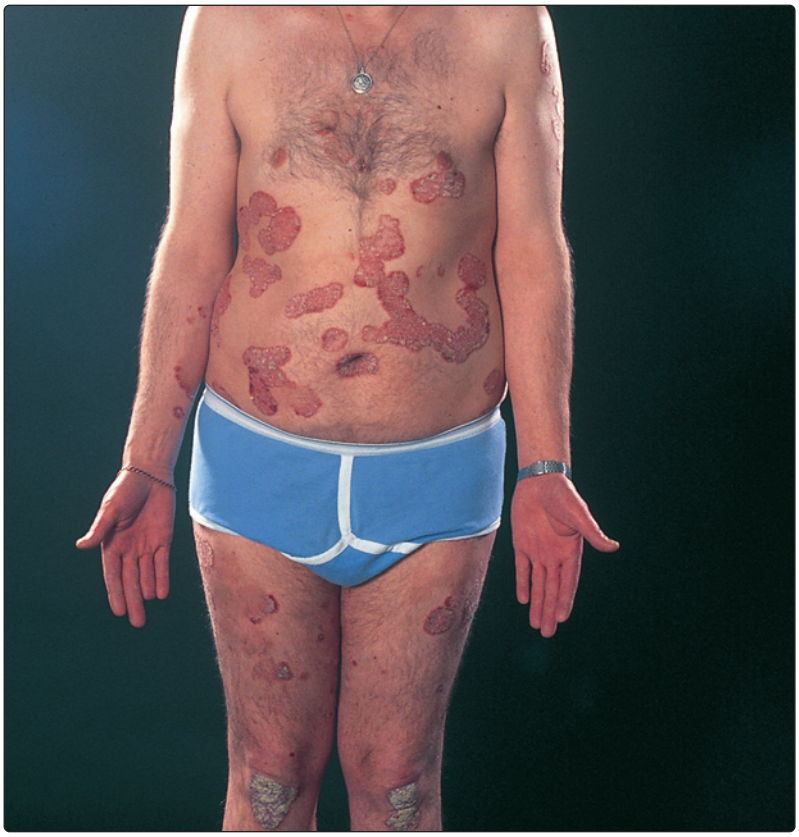


Fig. e14.1 Chronic plaque psoriasis on the trunk. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology. Mosby, with permission.)*

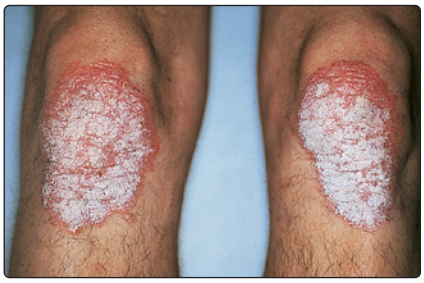


Fig. 14.3 Typical scaly plaques of psoriasis on the knees.

several centimetres, and are sometimes pruritic.

Guttate

Guttate psoriasis is an acute symmetrical eruption (a 'flurry') of 'drop-like' lesions with little scale in the early stage, usually on the trunk and limbs. This form mostly occurs in adolescents or young adults and may follow a streptococcal throat infection (Fig. 14.4).

- *Palmoplantar pustulosis* is characterized by yellow- to brown-coloured sterile pustules on the palms or soles (Fig. 14.6). A minority of subjects have classic plaque psoriasis elsewhere. It is most common in middle-aged women who are cigarette smokers, and it follows a protracted course.
- *Acrodermatitis of Hallopeau* is an uncommon indolent form of pustular psoriasis affecting the digits and nails (see Fig. 15.2).
- *Scalp psoriasis* may be the sole manifestation of the disease (see Fig. 15.1). It can be confused with dandruff but is generally better demarcated and more thickly scaled.
- *Napkin psoriasis* is a well-defined psoriasiform eruption in the nappy area of infants, few of whom later develop true psoriasis (p. 120).

Generalized pustular ✚

Generalized pustular is a rare but serious and even life-threatening form of psoriasis. Sheets of small, sterile yellowish pustules develop on an erythematous background and may spread rapidly (Fig. 14.7). The onset is often acute. The patient is unwell, with fever and malaise, and requires hospital admission.

Nail involvement

Psoriasis affects the matrix or nail bed in 25–50% of cases (Fig. 14.8). Thimble pitting is the commonest change, followed by *onycholysis* (separation of the distal edge of the nail from the nail bed). An oily or salmon pink discoloration of the nail bed is seen, often adjacent to onycholysis. Subungual hyperkeratosis, with a build-up of keratin beneath the distal nail edge, mostly affects the toenails. Nail changes are frequently associated with psoriatic arthropathy. Treatment is often difficult.

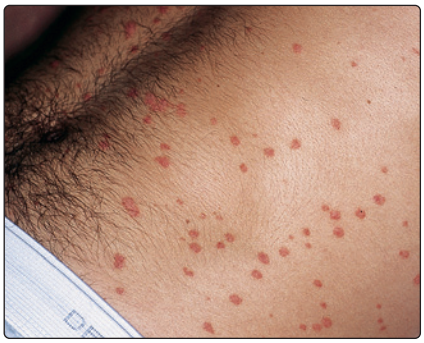


Fig. 14.4 The drop-like lesions of guttate psoriasis.

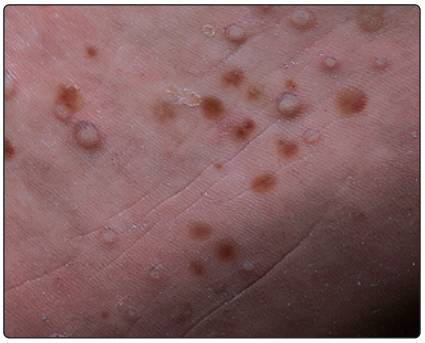


Fig. 14.6 Palmoplantar pustulosis: a localized variant of psoriasis on the sole of the foot.

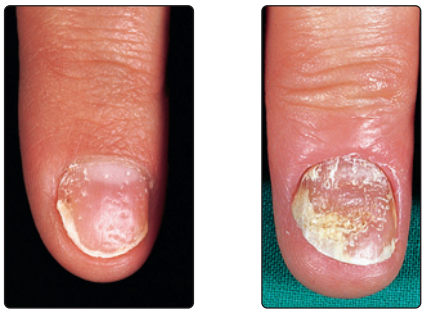


Fig. 14.8 Nail involvement in psoriasis: pitting (left) and subungual hyperkeratosis with onycholysis (right).

Flexural

This variant of psoriasis affects the axillae, submammary areas, groin, genitalia and natal cleft (Fig. 14.5). Plaques are smooth and often glazed but may be scaly. It is mostly found in the elderly.

Localized forms

Psoriasis can also present in a number of localized forms:

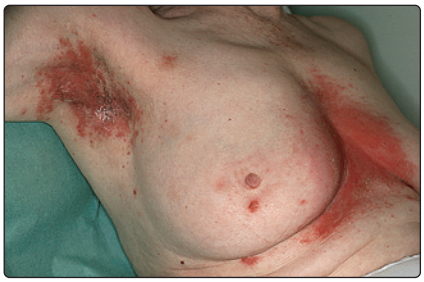


Fig. 14.5 Smooth, non-keratotic involvement in flexural psoriasis.

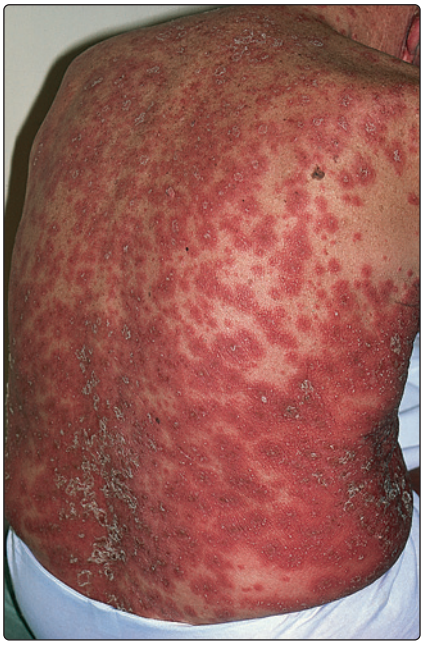


Fig. 14.7 Generalized pustular psoriasis in an elderly patient.

Psoriasis

- Psoriasis affects 1.5–3% of western populations.
- Inheritance is polygenic: 35% have a family history.
- Geneticists have identified loci for possible psoriasis genes, e.g. *PSOR1* on chromosome locus 6p.
- Peaks of onset are in the second to third and the sixth decades.
- The number of proliferating keratinocytes is increased seven-fold, but the epidermal cell cycle time is not shortened.
- Presentation is variable: the chronic plaque form affecting the elbows, knees and scalp is the commonest.
- Precipitating factors include streptococcal infection, drugs, sunlight, alcohol, smoking and psychological stress.
- Nail involvement is found in 25–50% of cases and is difficult to treat.

Guttate psoriasis is an acute symmetrical eruption (a 'flurry') of 'drop-like' lesions with little scale in the early stage, usually on the trunk and limbs. This form mostly occurs in adolescents or young adults and may follow a streptococcal throat infection (Fig. 14.4 and Fig. e14.2).

This variant of psoriasis affects the axillae, submammary areas, groin, genitalia and natal cleft (Fig. 14.5 and Fig. e14.3). Plaques are smooth and often glazed but may be scaly. It is mostly found in the elderly.

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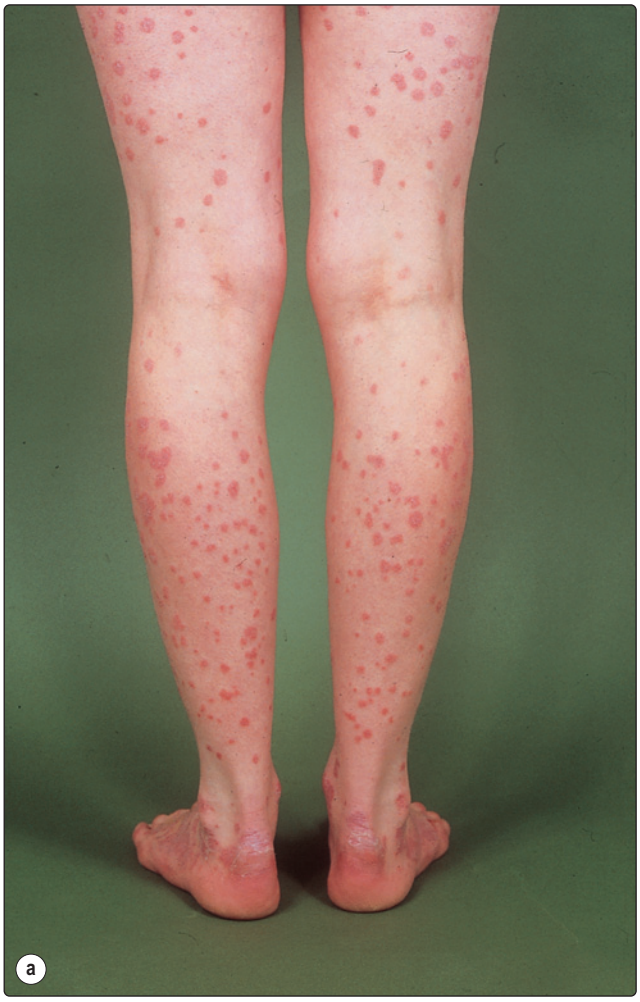
Generalized pustular is a rare but serious and even life-threatening form of psoriasis. Sheets of small, sterile yellowish pustules develop on an erythematous background and may spread rapidly (Fig. 14.7 and Fig. e14.5). The onset is often acute. The patient is unwell, with fever and malaise, and requires hospital admission.



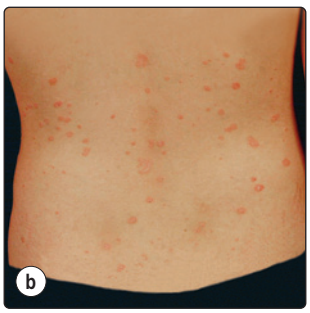


Fig. e14.2 Guttate psoriasis on the legs (a) and trunk (b) (some lesions of small plaque psoriasis are evident in addition). *(From Gawkrodger DJ 2004. Rapid Reference Dermatology. Mosby, with permission.)*

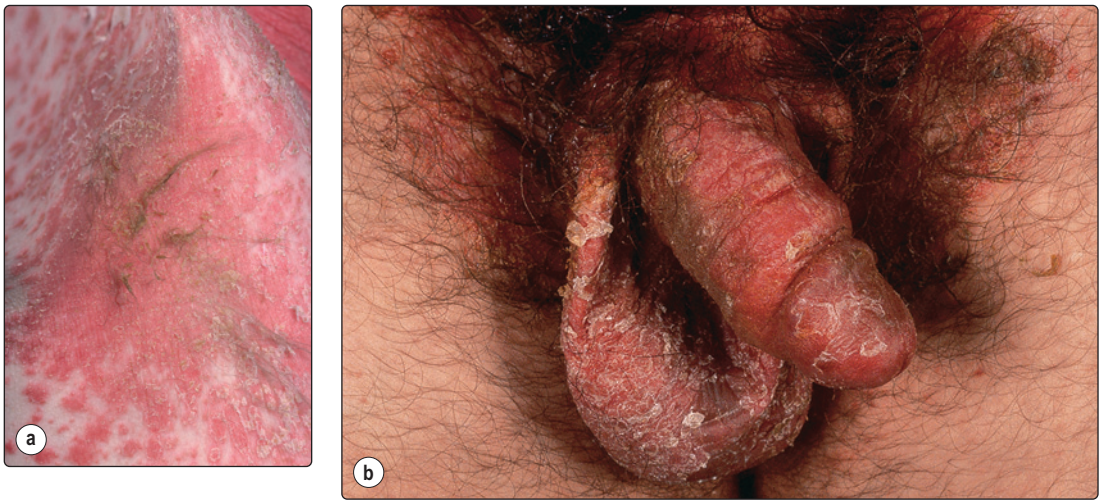


Fig. e14.3 Psoriasis of (a) the axilla and (b) the male genitalia showing erythematous plaques with scaling. The appearance may resemble seborrhoeic dermatitis. *(From (a) Gawkrodger DJ 2004. Rapid Reference Dermatology. Mosby; and (b) Bolognia JL, Jorizzo JL, Schaffer JV 2012. Dermatology, 3rd edn. Saunders, with permission.)*

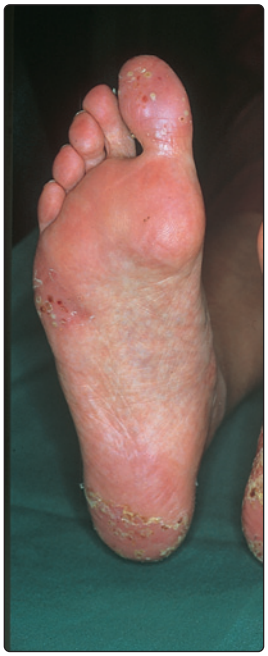


Fig. e14.4 Palmoplantar pustulosis showing yellow pustules on the big toe, the heel and the lateral forefoot. There is associated scaling. *(From Gawkrodger DJ 2004. Rapid Reference Dermatology. Mosby, with permission.)*

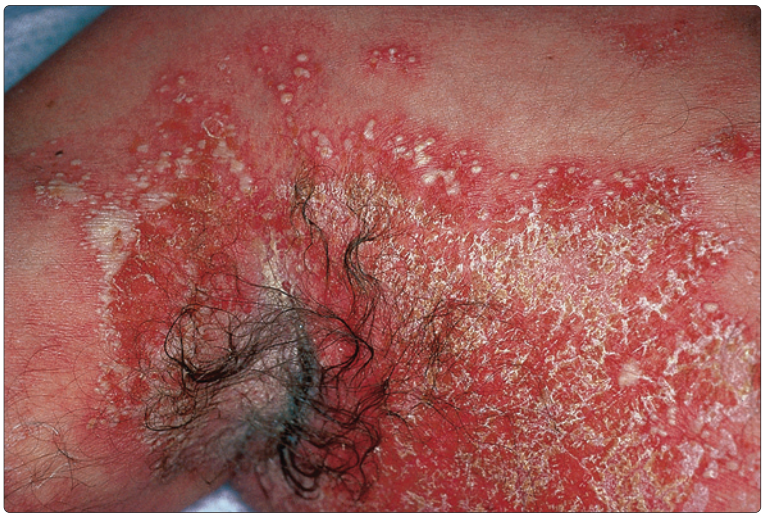


Fig. e14.5 Generalized pustular psoriasis. Within the area of erythema there are numerous pustules which in places have coalesced to form lakes of pus. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012. Dermatology, 3rd edn. Saunders, with permission.)*

Patient self-help organizations

Helpful patient-orientated advice can be obtained from the Psoriasis Association, the National Psoriasis Foundation and other similar organizations (access via https://www.psoriasis-association.org.uk/ and http://www.papaa.org/).

Further reading – online sources

A good recent review has been written by Langley and colleagues (Langley RGB, Krueger GG, Griffiths CEM 2005. Psoriasis: epidemiology, clinical features and quality of life. Ann Rheumatol Dis 64:18–25. Access via http://ard.bmj.com/).

Further reading – textbooks

The major textbooks such as Rook's Textbook and Bolognia, Jorizzo and Rapini, all have good sections on psoriasis as it is a bread-and-butter subject for dermatologists.

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van de Kerkhof, P.C.M. (Ed.), 2003. Textbook of Psoriasis, second ed. Blackwell, Malden.

15 | **Psoriasis** – Management and complications

Management

The non-infectious nature of psoriasis, its relapsing nature and the likely need for long-term therapy should be explained. A sympathetic approach is helpful, and patients often obtain support from the self-help group the Psoriasis Association (p. 31.e1). Treatment is tailored to the patient's particular requirements, taking into account the type and extent of the disease, and the age and social background (Table 15.1). NICE guidelines are a helpful guide.

Topical therapy

It is usual to prescribe topical agents as the first-line treatment.

Vitamin D analogues

Calcipotriol (Dovonex), *tacalcitol* (Curatoderm) and *calcitriol* (Silkis) are topical synthetic vitamin D analogues for use in mild and moderate chronic plaque psoriasis. They inhibit cell proliferation and stimulate keratinocyte differentiation, correcting some of the epidermal cell proliferation changes in psoriasis. Patient acceptability is good as the preparations do not smell or stain, are easy to apply and do not have the risk of skin atrophy seen with topical steroids. Skin irritation may be a problem. Efficacy is commensurate with dithranol or topical steroids.

Hypercalcaemia is possible if the maximum dose is exceeded. Calcipotriol cream can be used up to 100 g/week (40% of the body surface on a twice-daily basis), and tacalcitol ointment up to 35 g/week (20% of body surface as a once-daily dose). Tacalcitol is tolerated on the scalp and face, where calcipotriol tends to irritate. Calcipotriol is available as a scalp preparation. Vitamin D analogues are often used in alternation with a topical steroid, and in combination with ultraviolet B or psoralen plus ultraviolet A (PUVA) therapy.

Topical corticosteroids

Topical steroids have the advantage of being clean, non-irritant and easy to use. However, against this must be balanced the risk of side-effects (p. 23) and of precipitating an unstable form of psoriasis, especially on their withdrawal. Topical steroids are the treatment of choice for face, genitalia and flexures, and are useful for stubborn plaques on hands, feet and scalp. Potent steroids should not be applied to the face, although they may be used judiciously on palms and soles. Elsewhere, moderately potent steroids normally suffice. Their use must be monitored carefully. Creams are often preferred to ointments. Lotions and gels are available for the scalp.

Coal tar preparations

Coal tar distillates have been used for decades to treat psoriasis. They are safe and seem to act by inhibiting DNA synthesis. The main disadvantages of tar are that it smells and is messy. Despite this, it can be useful for inpatient care, e.g. combined with ultraviolet B – the Goeckerman regimen. Refined tar (1–10%) is available in a cream or lotion base for outpatient use (e.g. Carbo-Dome, Exorex, Psoriderm). These preparations are suitable for chronic plaque psoriasis or guttate psoriasis once the acute phase is past.

Dithranol (anthralin)

Dithranol has an antimitotic effect and is irritant to normal skin. It cannot be used on the face or genitalia, and it stains skin, hair, linen, clothes and bathtubs a purple-brown colour. For inpatient use, the usual base is Lassar's paste (zinc and salicylic acid paste BP). It is applied to the plaques of psoriasis initially in the 0.1% strength, increasing up to 2% if necessary. The surrounding skin is protected with a bland preparation such as white soft paraffin, and the treated area is covered with tube gauze. The combination of this with a daily tar bath and ultraviolet B is called the *Ingram regimen*. Psoriasis clears within 3 weeks in most patients on this treatment.

The 'short contact regimen', in which dithranol is applied for 30 min each day, is suitable for outpatients with stable plaque psoriasis. The dithranol is best washed off in a shower. Dithrocream is a suitable preparation and comes in concentrations from 0.1% to 2%.

Retinoids

A topical retinoid, tazarotene (0.05% and 0.1%; Zorac gel), is effective for chronic plaque psoriasis. It may irritate and is often used alternating with a topical steroid.

Keratolytics and scalp preparations

Hyperkeratotic psoriasis of the palms and soles can be treated with 5% salicylic acid ointment. Scalp psoriasis (Fig. 15.1) responds to 3% salicylic acid in a cream base (sometimes with 3% precipitated sulphur) applied daily or every 2–3 days, and is used in combination with a tar-containing shampoo (e.g. Alphosyl 2 in 1, Capasal, Polytar, T/Gel). Coconut oil compound (e.g. Cocois, with tar, salicylic acid and sulphur) also helps scaly scalps.

Systemic therapy

Psoriasis that is life-threatening, unresponsive to adequate topical treatment or restricting the ability to work (Fig. 15.2) may require systemic therapy. Benefits must be weighed against side-effects. The use of potentially toxic

Table 15.1 **A guide to psoriasis therapy**

Type of psoriasis	Treatment options
Stable plaque	Vitamin D analogue with topical steroid Dithranol (short contact), coal tar, tazarotene Narrow-band ultraviolet B
Extensive plaque	Narrow-band ultraviolet B (plus topicals) Methotrexate, ciclosporin, PUVA or Re-PUVA Biologics
Guttate	Topical steroids (mild/moderate), coal tar Narrow-band ultraviolet B
Facial/flexural	Topical steroids (mild/moderate); tacalcitol
Palmoplantar	Topical steroids (potent) Acitretin, PUVA or Re-PUVA
Generalized pustular; erythrodermic	Acitretin, methotrexate, ciclosporin Biologics

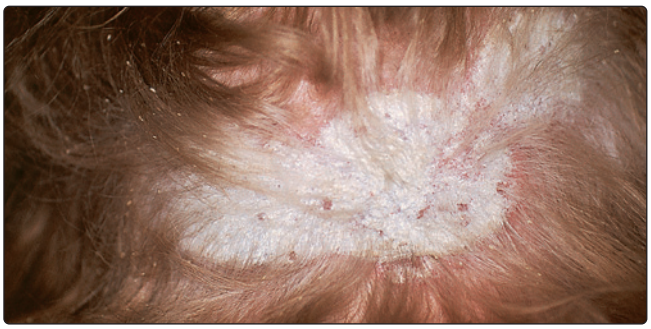

Fig. 15.1 Scaly plaques of psoriasis in the scalp, with localized hair loss.

The NICE guidelines are a good starting point for information about how to manage a patient's psoriasis if you are unsure of what to do, or the order in which treatments should be tried.

NHS Choices also provides an excellent overview with a video link (access via https://www.nice.org.uk/guidance/cg153 and http://www.nhs.uk/).

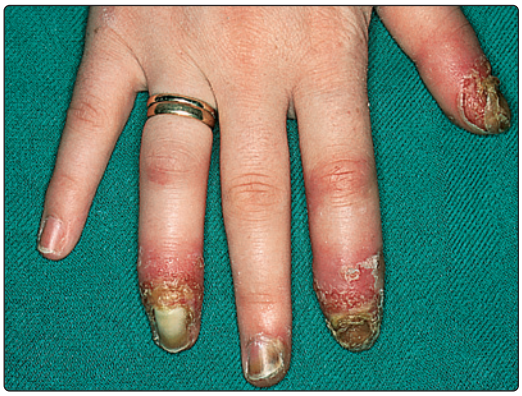

Fig. 15.2 Acrodermatitis continua variant of psoriasis. Sterile pustular changes with dactylitis are present on three fingers.

drugs is justified by their ability to transform a patient's life from severely restricted to nearly normal. Phototherapy and photochemotherapy are outlined on page 112.

Methotrexate

The folate antagonist methotrexate is well established as an effective treatment for severe psoriasis and may have antiinflammatory as well as immune modulatory effects. It is given once a week orally as a single dose (usually 7.5–15 mg), although it can be given subcutaneously or intramuscularly. Normal liver, kidney and bone marrow function must be established before starting methotrexate, and these functions must be monitored during treatment. Liver disease, alcoholism and acute infection are contraindications to methotrexate, and drug interaction (e.g. with aspirin, non-steroidal antiinflammatory drugs or co-trimoxazole) must be avoided. Improvement is seen within 2–4 weeks. Minor side-effects (e.g. nausea) are common, but liver fibrosis or cirrhosis is a risk long term. Liver damage can be monitored using the serum procollagen III aminopropeptide. Most authorities now regard the morbidity and cost of routine liver biopsy to be unjustified. Methotrexate is also a teratogen.

Retinoids

The vitamin A derivative acitretin (Neotigason) is particularly effective in treating pustular psoriasis and in thinning hyperkeratotic plaques. Acitretin may be used with topical therapies or with UVB or PUVA ('Re-PUVA'), when it allows a more rapid clearance at a lower total dose of UV. Most patients develop minor side-effects, such as dry mucous membranes, itching and peeling skin. More serious complications include hyperostosis, abnormal liver function, hyperlipidaemia and teratogenicity. The last virtually precludes the use of acitretin in women of child-bearing age. Although acitretin has a half-life of 50 days, in some patients it is metabolized to etretinate, a retinoid that takes 2 years to be excreted.

Ciclosporin

Ciclosporin, an immunosuppressant widely used to prevent rejection of organ transplants, is effective in severe psoriasis. It acts by inhibiting T lymphocyte activation and interleukin-2 production. Dose-dependent reversible nephrotoxicity is a side-effect. Blood pressure and kidney function are monitored during treatment. There may be a risk of skin cancer or lymphoma, and concomitant UV treatment is avoided.

Biologic agents and other systemic treatments

Other immunosuppressive drugs can control psoriasis, but they are not as potent as methotrexate. Hydroxycarbamide has the advantage of not affecting the liver, but it can suppress the bone marrow. Fumaric acid esters are effective in some cases. Biologic agents are very effective but expensive (see p. 32).

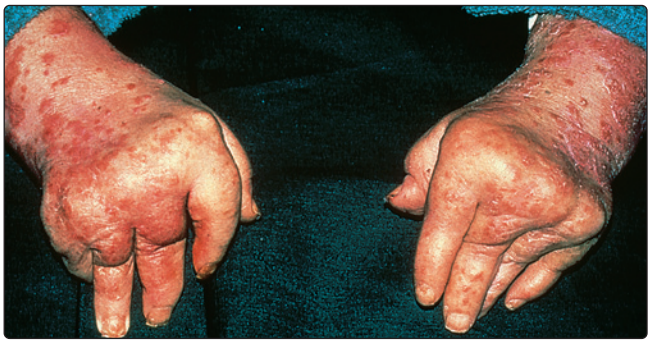

Fig. 15.3 Severe mutilating symmetrical arthritis with widespread psoriasis.

Complications

Psoriasis may be complicated by arthropathy, erythroderma and the Koebner phenomenon (Fig. 14.2). It is associated with the metabolic syndrome and an increased risk of cardiovascular disease. Assessment should be made for these conditions.

Psoriatic arthropathy

Psoriatic joint disease occurs in 20–30% of patients with psoriasis and is associated with more severe skin disease. It shows an equal sex ratio and takes three forms:

1. *Asymmetrical arthritis*. A small number of joints are usually involved, with few erosions and good preservation of function.
2. *Symmetrical polyarthritis*. This form is associated with erosions, deformity and loss of function (Fig. 15.3). It is distinguished from rheumatoid arthritis by predominantly affecting distal interphalangeal joints and by the rheumatoid factor test being negative.
3. *Predominant spondylitis*. This type is similar to ankylosing spondylitis and may be accompanied by a peripheral arthritis, although it behaves independently of it.

Erythrodermic psoriasis

Inpatient treatment is needed for this condition, often with systemic drugs. Details are given on page 47.

Treatment of psoriasis

The NICE guidelines are a good starting point. Side-effects are often the limiting factor in psoriasis treatment.

Topical treatment is usually the first approach:

- *Steroids*: popular and effective but beware of side-effects.
- *Vitamin D analogues*: clean and effective but may irritate.
- *Coal tar*: safe but messy and not very popular with patients.
- *Dithranol*: effective, irritant, rather impractical for home use.
- *Keratolytics*: useful for scalp disease combined with tar or sulphur.

Systemic treatment is used for serious or severe psoriasis:

- *PUVA*: popular but long-term risk of skin cancer.
- *Retinoids*: good for pustular psoriasis and as Re-PUVA; teratogenic.
- *Methotrexate*: a well-established systemic drug; hepatotoxic.
- *Ciclosporin*: effective but potentially nephrotoxic.
- *Biologics*: offer potential for targeted therapy; expensive.

Fumaric acid esters

Fumaric acid esters (such as Fumaderm) are occasionally used to treat moderate-to-severe psoriasis unresponsive to other therapies. They are a licenced medicine in some countries but not in the UK. Fumaric acid esters are thought to work by correcting imbalances in T cell immunity. It is usual to start with a low dose and then gradually work up to as high a dose within the recommended range as can be tolerated. The limiting factor in the use of fumaric acid esters is the side-effect profile, which includes flushing, headaches, nausea and gastrointestinal upsets. The monitoring of the full blood count for white cell count and of kidney and liver function is required.

Cardiovascular disease

Patients with psoriasis should be screened for arthritis, the presence of the metabolic syndrome and for cardiovascular disease in view of the increased prevalence of these conditions. Co-existent diseases may have an impact on the treatment that is appropriate and on response to therapy. More on these complications can be found at the Mayo Clinic website (access via http://www.mayoclinic.org/).

The metabolic syndrome

There is good evidence of a link between psoriasis and the metabolic syndrome (40% in psoriasis patients compared with 23% in the general population, in a North American study). The prevalences of obesity, diabetes mellitus, lipid abnormalities, cardiovascular disease and hypertension are higher in people with psoriasis than in the general population. This needs to be taken into account when assessing patients with psoriasis and when planning their treatments.

Patient self-help organizations

The Psoriasis Association (and similar organizations) provide excellent assistance to patients suffering with psoriasis (access via https://psoriasis-association.org.uk/ and https://www.psoriasis.org/).

Further reading – online sources

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Further reading – textbooks

The major textbooks such as Rook's Textbook and Bolognia, Jorizzo and Rapini, all have good sections on psoriasis as it is a bread-and-butter subject for dermatologists. Specialist books are also available:

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van de Kerkhof, P.C.M. (Ed.), 2003. Textbook of Psoriasis, second ed. Blackwell, Malden.

16 Psoriasis – Biologics

The biological response modifiers are breakthrough treatments for moderate-to-severe psoriasis and for other diseases such as rheumatoid arthritis and Crohn's disease. Biologics are based on recombinant cytokines, fusion proteins or monoclonal antibodies (mouse or human) that bind to tumour necrosis factor-α (TNF-α), cytokine receptors or block T cell receptors to have their effect (Fig. 16.1).

Scientific background

Research has confirmed psoriasis to be an immune-mediated inflammatory disease and has identified associated genes that are involved in immune regulation. These discoveries allow the pharmaceutical industry to design drugs that should work in psoriasis and in other diseases where the pathomechanisms are well understood (Fig. 16.2). The 'biologics' work by having a blocking effect on TNF-α, other cytokines (e.g. interleukin (IL)-12 and -23), dendritic cells and T lymphocytes involved in causing the disease. TNF-α is derived from Th1 cells and mediates inflammation by initiating a cascade of cytokines. IL-12 (derived from dendritic cells) and IL-23 are central to defining T helper cell types and T cell differentiation.

Effects of activated chronic inflammatory cytokines

The chronic inflammatory cytokines that are active in severe psoriasis may be one reason why patients with the disease have higher rates of cardiovascular morbidity. In addition, some genes associated with psoriasis may predispose to cardiovascular disease and diabetes.

Associated joint disease

Psoriasis is associated with an arthropathy in 20–30% of cases. Some but not all biologics will improve psoriatic arthritis in addition to the skin disease.

Types of biologic available

The most commonly used biologics for psoriasis are the anti-TNF-α agents *infliximab*, *etanercept* and *adalimumab*, and the anti-IL-12/IL-23 drug *ustekinumab*. The biologics are very effective drugs, producing better responses than agents such as methotrexate. They are given by i.v. infusion or s.c. injection, at intervals that vary from twice weekly to once every 3 months. The most commonly used biologics will be discussed individually (see online for fuller coverage).

- *Etanercept*: a fusion protein that acts by binding to soluble and receptor-bound TNF-α. It was the first biologic to be approved by the National Institute for Health and Clinical Excellence (NICE) for use in patients whose psoriasis is moderate to severe and has failed to respond to other systemic drugs such as ciclosporin and methotrexate, or photochemotherapy (PUVA). In psoriasis, the severity of skin involvement is measured by the Psoriasis Area and Severity Index (PASI; see p. 19) and the impact on a patient's life by the Dermatology Life Quality Index (DLQI; see p. 19). High scores on both of these parameters are required for the use and funding of this and other biologic drugs within the National Health Service in England, according to NICE. Etanercept is given by subcutaneous injection once or twice weekly (in a dose of 25 mg or 50 mg).
- *Adalimumab*: a human monoclonal antibody directed against TNF-α approved by NICE and administered by s.c. injection (40 mg every 2 weeks).
- *Infliximab*: a combined murine and human monoclonal antibody against TNF-α given by intravenous infusion at a dose of 5 mg/kg every 8 weeks. It is approved by NICE for severe psoriasis.
- *Ustekinumab*: this human monoclonal biologic blocks the p40 subunit common to IL-12 and IL-23. Ustekinumab is approved by NICE and is given by subcutaneous injection (45 mg or 90 mg for patients weighing

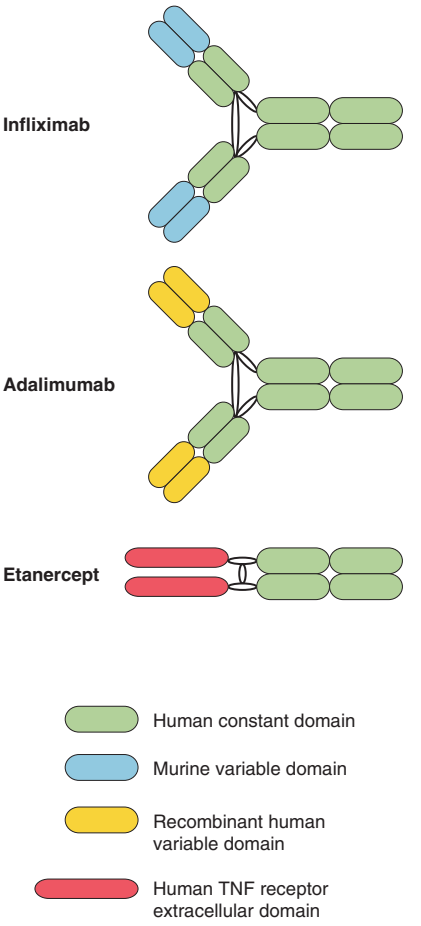

Fig. 16.1 Diagram of the structure of the biologics. Infliximab and adalimumab are similar to normal human immunoglobulins. Etanercept contains the extracellular TNF receptor domain fused to parts of the human immunoglobulin heavy chain.

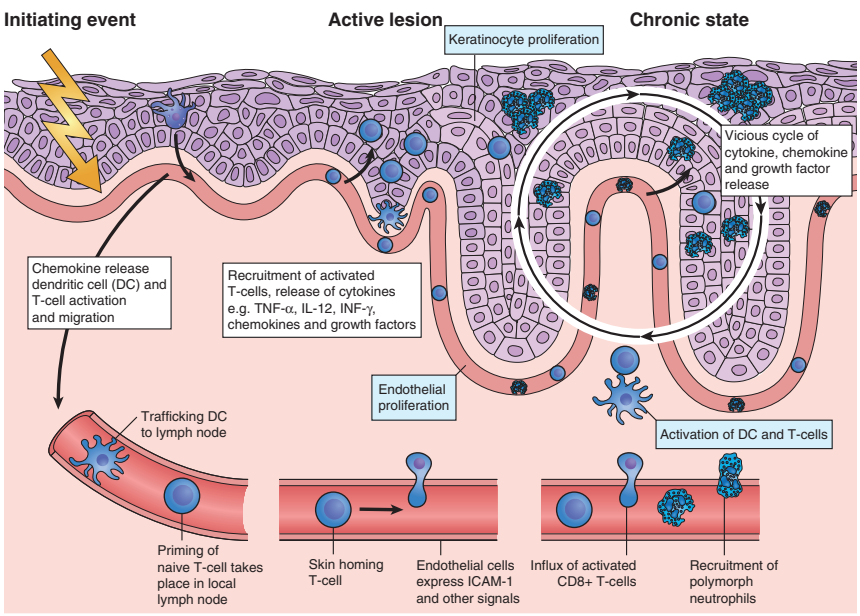

Fig. 16.2 A model of the immunopathogenesis of psoriasis. This illustration is showing the molecular and cellular changes as they progress from the initiating event through to the acute lesion and on to the chronic plaque. A vicious cycle of release of cytokines, chemokines and growth factors keeps the disease active. The biologics break the cycle by negating the inflammatory action of TNF-α, IL-12 and other factors.

The biologics have revolutionized the management of psoriasis and allowed many patients to maintain a good quality of life. Lengthy and costly hospital admissions for inpatient topical therapy combined with phototherapy are virtually a thing of the past. Detailed information on when and how to use biologics in the treatment of psoriasis can be found on the Psoriasis Association and NICE websites (access via: https://www.psoriasis-association.org.uk/ and http://www.nice.org.uk/).

>100 kg) every 12 weeks after a loading regimen.

Pretreatment screening

Prior to initiating treatment, patients are counselled about potential side-effects of biologics (see below) and screened for other risk factors, as follows:

- Detailed history to exclude past or present cardiovascular or demyelinating disease and serious infections.
- Note the presence of coexisting joint disease that may influence the selection of biologic.
- Screen for infections including viral hepatitis, HIV and tuberculosis (the latter by chest X-ray and interferon-gamma release assay).
- In females of child-bearing age, exclude pregnancy.

Effectiveness of biologics

The biologics show varying degrees of effectiveness in treating psoriasis. Response to treatment can be compared by looking at the proportion of patients treated who achieved a 75% improvement in their PASI score (the 'PASI 75') after 10–12 weeks of biologic therapy (Fig. 16.3). If there has been no response after 12–16 weeks, the drug is withdrawn or changed. Etanercept, adalimumab and infliximab are also effective in psoriatic arthritis.

Therapeutic algorithm

Biologics are approved by NICE (in the UK) for use in patients with severe psoriasis who have a PASI >10 and a DLQI >10, and who have failed on (or are intolerant of) standard systemic treatments such as ciclosporin, methotrexate or PUVA. Etanercept, adalimumab and ustekinumab are all approved for use in this situation. If the psoriasis is very severe, infliximab may be the most appropriate, as it seems to have a more rapid onset of action. Occasionally methotrexate is used in combination with etanercept or infliximab. Patients who have failed on one biologic may be tried on an alternative. Ustekinumab may be an appropriate alternative to etanercept or adalimumab due to its different mode of action.

Side-effects of biologics

The main problems with biologics are related to injection site reactions, serious infections (e.g. reactivation of latent tuberculosis), cancers, demyelination and cardiovascular events. Occasionally biologics actually cause a worsening of psoriasis. They are expensive in comparison with other treatments. Generally the biologics are well tolerated by patients.

Use of biologic agents in other skin diseases

These are detailed in Table 16.1.

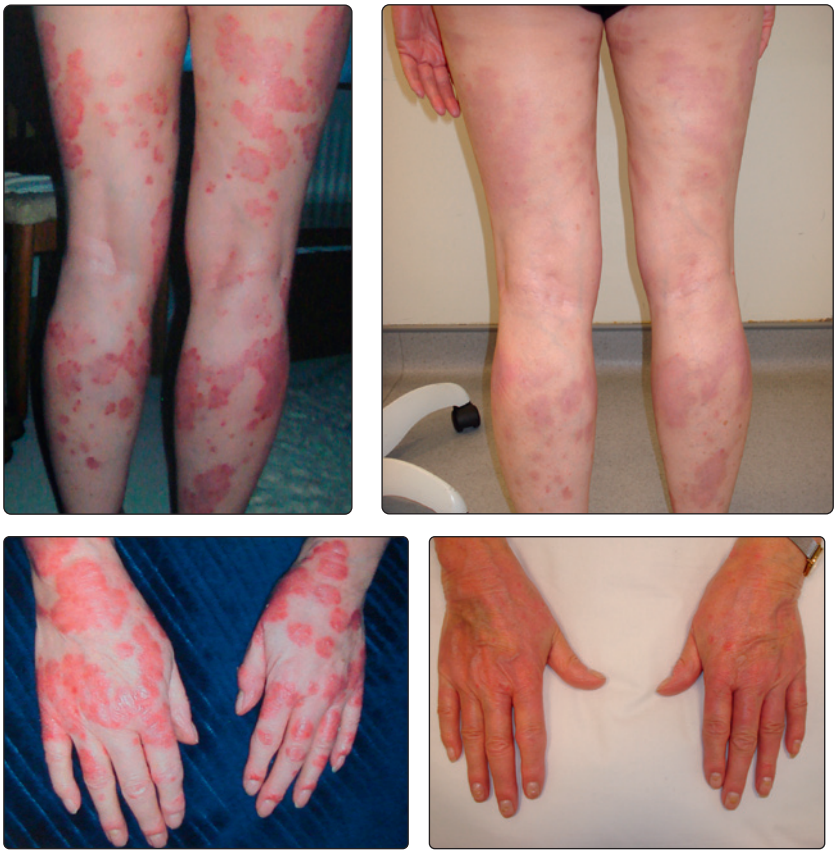

Fig. 16.3 Significant improvement can be seen in a patient treated with a biologic in these before and after images.

Table 16.1 **Use of biologics in other skin diseases**

Biologic	Type	Disease treated
Rituximab	IgG chimeric antibody directed against CD20 that potently depletes B cell numbers Given as an intravenous infusion	Used successfully in B cell malignancies and in autoimmune diseases including systemic lupus erythematosus, dermatomyositis, systemic sclerosis and pemphigus
Infliximab	Combined murine and human monoclonal antibody against TNF-α	Beneficial off-licence use in hidradenitis suppurativa, pyoderma gangrenosum, sarcoidosis, Behçet's disease and certain types of vasculitis
Omalizumab	Humanized monoclonal antibody that binds to IgE and thus inhibits the binding of IgE to high-affinity receptors on mast cells and basophils	Use is being considered in chronic urticaria (by NICE) and in atopic dermatitis Preliminary results are said to be mixed

Biologics

- **Exciting new class of immunologically active drugs:** biologics are selectively directed against the molecular pathways known to be involved in the pathogenesis of psoriasis.
- **Properly controlled clinical trials:** have demonstrated the efficacy of these agents in reducing the severity and extent of psoriasis and in improving quality of life.
- **NICE approval:** in the UK, etanercept, adalimumab and ustekinumab can be used in patients with moderate-to-severe psoriasis who have appropriate PASI and DLQI scores.
- **Infliximab infusion:** is approved for use in more severe cases of resistant psoriasis.
- **Administration:** biologics are given by subcutaneous injection or intravenous infusion. The frequency of dosing is very variable, ranging from twice weekly to once every 3 months.
- **Infliximab in other diseases:** off-licence reports indicate infliximab to be beneficial in severe cases of pyoderma gangrenosum, hidradenitis suppurativa and sarcoidosis.
- **Rituximab:** a biologic that depletes B cells. It can be beneficial in pemphigus and some autoimmune diseases (off-licence use).
- **Atopic eczema:** to date, there are no biologics approved for use in atopic eczema.

Biologics are approved by NICE (in the UK, www.nice.org) for use in patients with severe psoriasis who have a PASI >10 and a DLQI >10, and who have failed on (or are intolerant of) standard systemic treatments such as ciclosporin, methotrexate or PUVA. Etanercept, adalimumab and ustekinumab are all approved for use in this situation. If the psoriasis is very severe, infliximab may be the most appropriate, as it seems to have a more rapid onset of action. Occasionally methotrexate is used in combination with etanercept or infliximab. Patients who have failed on one biologic may be tried on an alternative. Ustekinumab may be an appropriate alternative to etanercept or adalimumab due to its different mode of action.

℞ New drugs for psoriasis

New drugs for psoriasis of novel mechanisms of action are regularly becoming available at the moment.

- *Secukinumab* (Cosentyx), a fully human anti-interleukin-17A monoclonal antibody, given monthly by subcutaneous injection (after a loading dose of 4 weekly injections) has been shown to be superior in terms of the proportion of patients with moderate-to-severe plaque psoriasis achieving a PASI 90 score (that is a reduction of ≥90% in their PASI score from baseline) after 8, 12 and 16 weeks, when compared with ustekinumab. In a clinical trial, 79% of those receiving secukinumab achieved PASI 90 at 16 weeks compared with 58% receiving ustekinumab.
- *Apremilast* (Otezla), a phosphodiesterase-4 (PDE4) inhibitor taken orally (as 30 mg twice daily), is effective for moderate-to-severe nail and scalp psoriasis. Over a 16-week period of taking apremilast, 47% of patients were clear of (or only had minimal) scalp psoriasis compared with 18% who responded to placebo.
- *Janus kinase inhibitors* such as ruxolitinib and tofacitinib have been approved for use in psoriasis in the United States but are not yet available in Europe. The Janus kinase ('JAK') family of enzymes are responsible for the signal transduction that mediates the function of cytokine receptors.

Further reading – online sources

A good recent review has been written by Langley and colleagues (Langley RGB, Krueger GG, Griffiths CEM 2005. Psoriasis: epidemiology, clinical features and quality of life. Ann Rheumatol Dis 64:18–25. Access via http://ard.bmj.com/).

Further reading – textbooks

The major textbooks such as Rook's Textbook and Bolognia, Jorizzo and Rapini, all have good sections on psoriasis as it is a bread-and-butter subject for dermatologists.

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van de Kerkhof, P.C.M. (Ed.), 2003. Textbook of Psoriasis, second ed. Blackwell, Malden.

17 | Eczema – Basic principles and irritant contact dermatitis

Definition

Eczema is a non-infective inflammatory skin condition that shows itching, redness, papulation and scaling. Eczema represents a reaction pattern to a variety of stimuli, some of which are recognized but many of which are unknown. Eczema and dermatitis mean the same thing and may be used interchangeably.

Classification

The current classification of eczema is unsatisfactory in that it is inconsistent. However, it is difficult to provide a suitable alternative as the aetiology of most eczemas is not known. Different types of eczema may be recognized by morphology, site or cause. A division into endogenous (due to internal or constitutional factors) and exogenous (due to external contact agents) is convenient (Table 17.1). However, in clinical practice, these distinctions are often blurred and, not infrequently, the eczema cannot be classified. A further division into acute (Fig. 17.1) and chronic (Fig. 17.2) eczema can be made in many cases according to the morphology of the eruption.

Table 17.1 **A classification of eczema**

Type	Variety
Exogenous (contact)	Allergic, irritant Photoreaction
Endogenous	Atopic Seborrhoeic Discoid (nummular) Venous (stasis, gravitational) Pompholyx
Unclassified	Asteatotic (eczema craquelé) Lichen simplex (neurodermatitis) Juvenile plantar dermatosis

Acute eczema

In acute eczema, epidermal oedema (spongiosis), with separation of keratinocytes, leads to the formation of epidermal vesicles (Fig. 17.3a). Dermal vessels are dilated, and inflammatory cells invade the dermis and epidermis.

Chronic eczema

In chronic eczema, there is thickening of the prickle cell layer (acanthosis) and stratum corneum (hyperkeratosis) with retention of nuclei by some corneocytes (parakeratosis) (Fig. 17.3b). The rete ridges are lengthened, dermal vessels dilated and inflammatory mononuclear cells infiltrate the skin.

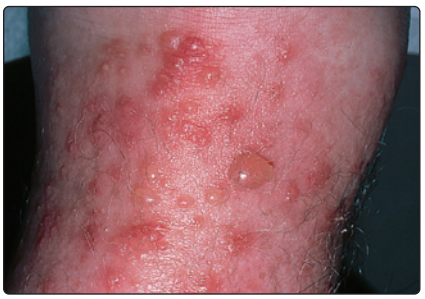


Fig. 17.1 Acute dermatitis (eczema). Erythema and oedema are seen with papules, vesicles and sometimes large blisters. Exudation and crust formation follow. The eruption is painful and pruritic. This case resulted from a contact allergy to a locally applied cream.

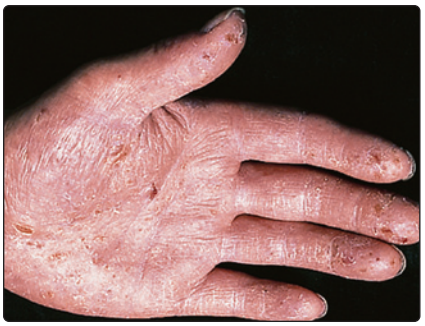


Fig. 17.2 Chronic dermatitis (eczema). Lichenification, scaling and fissuring of the hands due to repeated exposure to irritants. Allergic contact dermatitis cannot be excluded on the appearance alone.

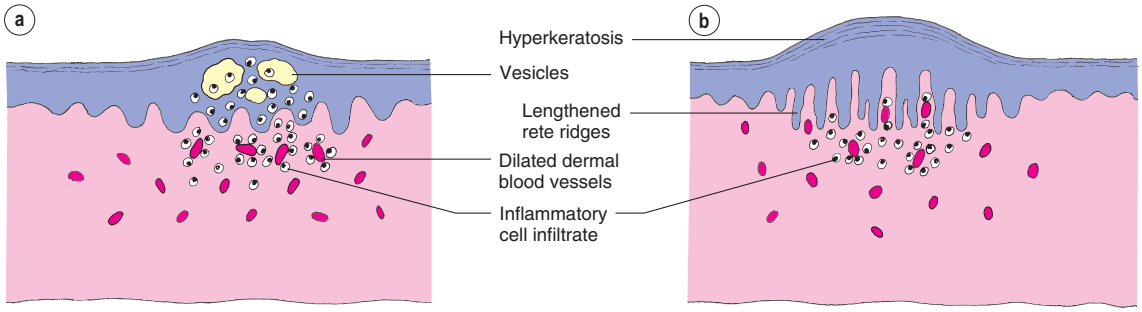


Fig. 17.3 The histology of (a) acute and (b) chronic dermatitis.

Irritant contact dermatitis

Definition

Dermatitis precipitated by an exogenous agent, often a chemical, is known as contact dermatitis. It is particularly common in the home, among women with young children and in industry, where it is a major cause of loss of time from work (see p. 132). Contact dermatitis may be due to the effects of irritants or allergens, or a combination of the two, often with contribution from endogenous factors. When contact dermatitis is suspected, patch testing is mandatory, as it is very difficult to exclude an allergic cause on clinical grounds alone (see Ch. 18). Non-allergic triggers of inflammation in the skin mediate irritant contact dermatitis. Irritants cause more cases of contact dermatitis than allergens, although the clinical appearances are often similar.

Aetiopathogenesis

Although, it seems that the threshold for irritancy differs between individuals, irritant reactions can be induced in anyone given adequate exposure to the irritant and is not dependent upon immunological memory. Further distinction from allergic responses is noted by the fact that irritant reactions can happen at first exposure (whereas allergic responses take 5–7 days before induction). However, many irritant reactions are identified after prolonged exposure with presumed gradual accumulation of the

The current classification of eczema is unsatisfactory in that it is inconsistent. However, it is difficult to provide a suitable alternative as the aetiology of most eczemas is not known. Different types of eczema may be recognized by morphology, site or cause (Table e17.1). A division into endogenous (due to internal or constitutional factors) and exogenous (due to external contact agents) is convenient (Table 17.1). However, in clinical practice, these distinctions are often blurred and, not infrequently, the eczema cannot be classified. A further division into acute (Fig. 17.1) and chronic (Fig. 17.2) eczema can be made in many cases according to the morphology of the eruption.

Table e17.1 **The Eczmas**

'The eczemas'	Prevalence	Sex predisposition	Age of onset	Pathogenesis	Syptoms	Pattern	Treatment principles	Complications	Prognosis
Atopic eczema	10-30% children; 2-10% adults	Equal	>50% under 2 yrs	Large genetic contribution, with dominant role of mutations in gene encoding filaggrin. Allergic responses play a role in disease flares.	Severe itch, often precluding sleep	Prominent involvement of flexures, but can be widespread. Often also the face and ands. Usually spares nose. Erythema, papules and scaling. Secondary excoriations, lichenification, and infection may also be seen.	Avoidance of triggesrs (including irritants and allergens), reparation of skin barrier (emollients), anti inflammatories (topical corticosteroids, topical calcineurin inhibitors) and anti-infectives (as indicated).	Skin infections (bacteria e.g. S. aureus; virus e.g. Herpes simplex; fungus e.g. Malassezzia furfur)	Generally improves with age
Allergic contact dermatitis	20% of the adult population are allergic to at least one contact allergen (most common nickel and fragrance, but increasingly methylchloroisothiazolinone)	Females more common	Adult	Not thought to have a large genetic component. Environmental exposure to allergenic chemcals is causative.	Itch, occasionally painful during severe reactions	Often well demarcated to area of allergen exposure (e.g. unilateral). However, often also hard to distinguish from atopic eczema. Certain sites show increased predisposition (e.g. Face, genitals, hands, chronic wounds)	Avoidance of causative allergen	Secondary spread of eczema to non-exposed sites or systemic reactions may arise in severe cases	Resolves completely with allergen avoidance. Occupational allergic contact dermatitis may require career change.
Seborrhoeic dermatitis	5% prevalence, but lifetime incidence much higher	Males more common	Infancy (<3 months) and adulthood (40-60 years)	Linked to overgrowth of natural yeast commensals (e.g. Malassezia furfur) and sebum production. Exacerbated in HIV and Parkinson's disease	Nil or minimal itch	Infancy - ususally scalp involvement (cradle cap); plus variable skin (often flexures) and napkin area involvement; Adult - usually scalp with variable face (eyebrows, nasolabial folds) and sternal involvement	Mild topical corticosteroids are used in the acute stages, but maintenance treatment is with anti-yeast therapy (imidazoles) as shampoo or creams and emollients	Not usually secondarily infected	Infantile disease usually resolves, whereas adult disease is usually relapsing and remitting
Discoid eczema	0.1-9.1%	Younger (<30 yrs) patients more commonly females; older patients more commonly male	Most commonly after 50 yrs	Unclear, some may be triggered by local skin infections	Severe itch	Round (disc shaped) patches of eczema, usually confined to the legs and sometimes arms	Topical corticoisteroids and calcineurin inhibitors are usually efective. Sometimes phototherapy or systemic treatment may be required.	Secondary infections are seen (usally S. aureus)	
Venous eczema	Common amongst the 15% of adults who suffer venous insufficiency	Equal	Elderly	Venous hypertension, often due to valvular incompetence, leads to lower leg tissue oedema and extravasation of erythrocytes. This leads to chronic inflammation and itch.	Itch	Usually bilateral, confined to the lower legs, with evident signs of venous hypertension.	Topical corticosteroids help the acute inflammation, but maintenance treatment requires the venous incompetence to be addressed e.g. compression). Daily emollients are helpful.	Venous ulceration is not a direct complication of the venous eczema, but may arise following trauma through scatching in atrophied skin. Prevalence of allergic contact dermatitis is increased in venous eczema.	Without correction of the underlying vascular defects, gradual deterioration is seen

Asteatotic eczema	Moderate-severe disease is uncommon, but mild disease is probably common	Equal	Elderly	All skin dries with age, but low humidity, exposure to soaps, poor nutrition and impaired renal function are implicted in preciptating this condition. Probably mediated by defects in stratum corneum composition.	Mild-moderate disease often not itchy.	Initially, involves lower legs with criss-crossed cracks and faissues in generalised dry skin. Can spread to other areas.	Intense emollient therapy. Corticosteroids are not required.		Responds well to treatment.
Irritant contact dermatitis	Estimated 1-2% population	Females more common	Any age, but infants and elderly more common	Epidermal damage is central. Acute toxicity to keratinocytes (e.g. bleaches) or chronic damage to barrier by removal of lipids (e.g. solvents and detergents) account for different patterns of onset. Water exposure induces barrier disruption.	Itch and sometimes pain inn acute cases	Restricted to area of irritant exposure. Often hard to distinguish from allergic contact dermatitis. Certain sites show increased predisposition (e.g. hands, finger webs).	Avoidance of irritants if possible, regular emollient use and short term corticosteroid application are likley to be helpful.		Often difficult to treat. Occupational irritant contact dermatitis may require career change.
Pompholyx eczema	Estimated 0.1% population	Equal	Young adults most common	Usually co-exists with atopic eczema. Rarely, may be assocaited with tinea infections. Sweating is also a frequent exacerbator.	Severe itch arises at the onset of vesiculation, which gradulaly resolves typically over the course of a week and then leads to scaling and often fissuring. This may be a cyclical problem.	Classically, vesicles arise on the lateral margins of the fingers. However, more severe cases may involve the palms and soles.	Potent topical corticosteroids at the outset of vesiculation are beneficial. Potassium permanganate soaks may also be beneficial. More severe cases may need intermittent systemic treatment.	Following vesiculation, the onset of fissures may be complicated by secondary infection.	Often prolonged problems for several years, but disease remission usually follows.
Juvenile plantar dermatosis	Rare	Boys more common	3-13 yrs	Typically arises in individuals with atopic background in winter. Exacerbated by occlusive footwear and following friction to the feet.	Discomfort due to cracking. Itching less prominent.	Dryness and scaling restricted to the ball of the feet and plantar surface of toes.	Emollient and breathable shoewear are helpful.	Infection may arise in fissures	Generally improves with age

irritant signals. It is likely that irritant reactions are mediated by the innate immune system, which senses barrier disruption and noxious substances in the skin. The most important irritants are described in Table 17.2.

A strong irritant causing necrosis of epidermal cells will produce a reaction within hours but, in most cases, the effect is more chronic (Table 17.3). Repetitive and cumulative exposure over several months or years to water, abrasives and chemicals can induce dermatitis, commonly on the hands. Individuals with a history of atopic eczema are more susceptible to irritants.

Table 17.2 **The occupational sources of common irritants**

Occupation	Source
Builders	Cement, friction
Cleaners	Detergents, solvents
Cooks	Meat, vegetables, soaps
Hairdressers	Shampoos, bleach
Healthcare workers	Water, soaps
Metal workers	Cutting oils, water
Office workers	Paper, dry air
Farmers	Animal secretion

(Adapted from English J, Aldridge R, Gawkrodger DJ et al. 2009. Clin Exp Dermatol 34:761–769.)

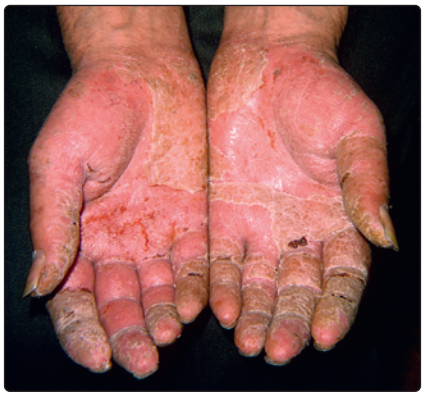


Fig. 17.4 Irritant contact dermatitis of the hands secondary to repeated exposure to solvents. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Clinical presentation

Irritant contact dermatitis may affect any part of the body, although the hands are the most common sites (Fig. 17.4). As with allergic contact dermatitis, the patient's occupation, hobbies, and daily routine helps in identifying possible causes.

Differential diagnosis

Irritant contact dermatitis of hands must be differentiated from allergic contact dermatitis, endogenous eczema, latex contact urticaria (p. 133), psoriasis and fungal infection.

Management

The management of irritant contact dermatitis is not always easy because it frequently requires significant lifestyle changes to avoid wet work, etc. *Patch testing* (p. 36) is critical to exclude allergic components especially for dermatitis of the face, hands and feet (Fig. 17.5). The avoidance of the suspected irritant is required to resolve the problem. However, irritants are often impossible to exclude. Some contact with irritants may be inevitable owing to the nature of certain jobs, but occupational hygiene can often be improved. Unnecessary contact with irritants should be limited, protective clothing worn (notably nitrile gloves) and adequate washing and drying facilities provided. *Barrier creams* are seldom the answer, although they do encourage personal skin care. *Topical steroids* (moderately potent or potent) help in irritant contact dermatitis, but avoidance measures should predominate. Standard advice for hand eczema is summarized in Table 17.4.

Table 17.3 **Common and virtually ubiquitous irritants**

water and other fluids	solvents, soaps and detergents
abrasives, i.e. frictional irritancy	cosmetics, personal care products.
chemicals, e.g. acids and alkalis	

Table 17.4 **Management of irritant contact dermatitis of the hands**

Personal care	Deodorants and antibacterial soaps and cleansers should not be used. Vinyl gloves can be worn to shampoo hair.
Hand washing	Avoid hand washing. Use lukewarm water only. Avoid stringent/scented soaps. Instead use emollient cleansers (soap-free). Remove rings before wet work or hand washing.
Drying	Pat rather than rub the hands dry.
Emollients	Apply emollients after washing. Ointments are more effective than creams.
Housework	Avoid using household cleansers. Cotton gloves can be useful for general housework, and gardening gloves for heavy work to avoid the need for hand washing. Dishes should be washed with a long-handled brush rather than a cloth to avoid wetting hands. Use of a dishwasher instead of hand washing is recommended.
Temperature/ sweating	Excessive heating or cooling is irritant to the skin. Occlusion caused by gloves can cause sweating, which is also irritant. To minimize occlusion, cotton gloves may be worn inside loose-fitting rubber or vinyl gloves.
Food	Reduce skin contact with fruit juice, fruits, vegetables, raw meat, onion and garlic.

(Adapted from English J, Aldridge R, Gawkrodger DJ et al. 2009. Clin Exp Dermatol 34:761–769.)

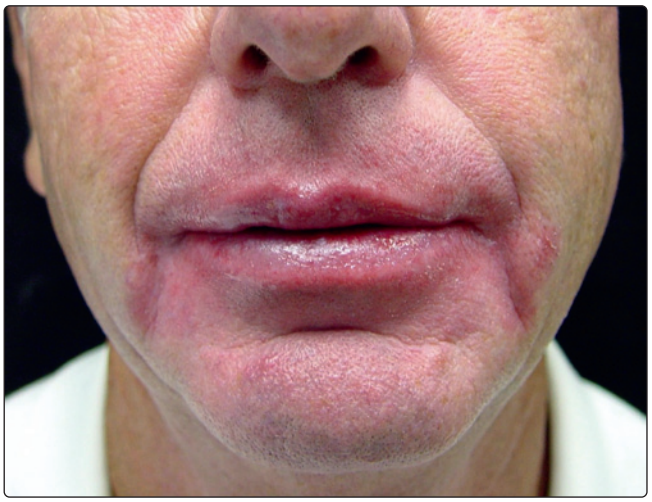


Fig. 17.5 Irritant cheilitis due to lip lick habit. Patch testing is needed to exclude an allergic cause. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Irritant contact dermatitis

- **Irritant factors of various types** cause more contact dermatitis than allergens.
- **Irritant contact dermatitis,** can be difficult to distinguish from allergic or endogenous eczema on morphology grounds alone.
- **Atopics and those with 'a sensitive skin'** are more susceptible to the effects of irritants.
- **Patch testing** is helpful to exclude allergic contact dermatitis.
- **Common irritants:** water, frictional abrasives, chemicals (especially alkalis), solvents, oils, detergents, soaps, low humidity and temperature extremes.
- **Management of irritant dermatitis** often requires a significant change in lifestyle, especially the avoidance of wet work and of exposure to soaps, detergents and frictional abrasion, with use of emollients and occasionally topical steroid ointments.

(see Self-assessment exercise).

Further reading – online sources

More information is available at the website of the British Society for Cutaneous Allergy (access via http://www.cutaneousallergy.org/), from which patient information sheets may also be downloaded.

Further reading – textbooks

Readers are referred to specialized texts such as:

Chew, A.-L., Maibach, H.I. (Eds.), 2006. Irritant Dermatitis. Springer, Berlin.

Johansen, J.D., Frosch, P.J., Lepoittevin, J.P. (Eds.), 2011. Contact Dermatitis, 5th ed. Springer, Berlin.

18 Eczema – Allergic contact dermatitis and patch testing

Definition

Allergic contact dermatitis is an eczema precipitated by an exogenous agent, often a chemical, which is recognized by the immune system as an antigen and results in T cell mediated inflammation. Often, irritant and endogenous factors are also involved in the clinical picture.

Aetiopathogenesis

Individual predisposition to allergic contact dermatitis varies. Similar exposures to chemicals in cosmetics, medicinal products or environmental allergens give rise to allergic reactivity in some and not in others. Certain people develop allergy following low level exposure while in others, multiple hypersensitivities occur. However, there is little to support a genetic effect.

Induction of an allergic response is initiated through the skin. Chemical antigen is bound to self-proteins on, and processed by, skin dendritic cells, which migrate it to the draining lymph node for presentation to naive CD4+ T lymphocytes. Within 5–7 days or longer, these specific effector T cells leave the lymph node and return to the skin under skin-homing molecular control where, when the chemical allergen is re-encountered, inflammation is induced producing dermatitis.

Clinical presentation

Allergic contact dermatitis may affect any part of the body, although the hands and face are common sites. The appearance of a dermatitis at a particular location (Fig. 18.1) can suggest contact with certain objects. For example, an eczema on the wrist of a woman with a history of reacting to cheap earrings suggests a nickel allergic response to a watchstrap buckle (Fig. 18.2). Diagnosis is often not easy as a history of allergen exposure is not always forthcoming. Knowing the patient's occupation, hobbies, past history, use of cosmetics or medicaments, contact with household agents and work-related exposures helps in listing possible causes. Environmental sources of common allergens are shown in Table 18.1. Medicaments (p. 22), cosmetics (p. 118), household items, plants and workplace exposures (p. 132) can all induce allergic and irritant reactions.

Allergic contact dermatitis occasionally becomes generalized by secondary 'autosensitization' spread. Activation by ultraviolet (UV) radiation of a topical agent, e.g. UV sunscreen filters or previously some perfumes, produces a photocontact reaction in sun-exposed sites (p. 49; Fig. e18.2).

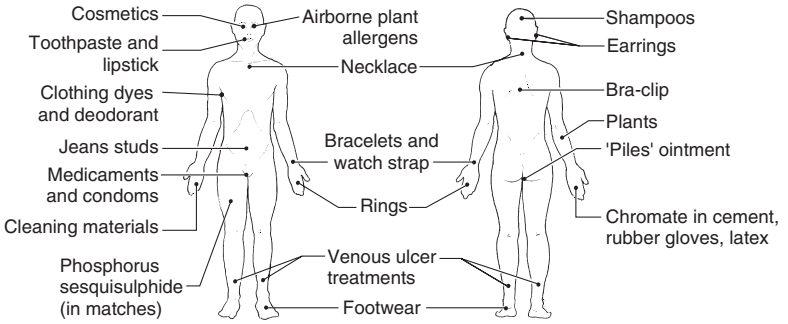


Fig. 18.1 Distribution clues for allergic contact dermatitis.

Table 18.1 **The sources of common allergens**

Allergen	Source
Chromate	Cement, tanned leather, primer paint, anticorrosives
Cobalt	Pigment, paint, ink, jewellery, metal alloys
Colophonium	Glue, plasticizer, adhesive tape, varnish, polish
Epoxy resins	Two-component adhesives, cast mouldings
Fragrances	Cosmetics, creams, soaps, deodorants, household products, aromatherapy
Nickel	Jewellery, zips, fasteners, scissors, instruments
Para-phenylenediamine	Hair dye, clothing dye, shoes, colour developer
Plants	*Primula obconica*, chrysanthemums, garlic, poison ivy/oak (USA)
Preservatives	Cosmetics, creams and oils, paints, coolant oils
Rubber chemicals	Gloves, clothing, shoes, masks, tyres, condoms

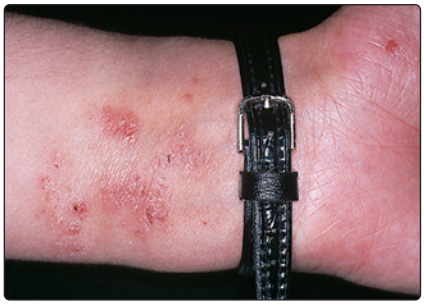


Fig. 18.2 Allergic contact dermatitis to nickel in a watchstrap buckle.

Differential diagnosis

Allergic causes of contact dermatitis need to be differentiated from irritant ones, although often the two coexist. Endogenous eczema, latex contact urticaria (p. 80), psoriasis and fungal infection may also require consideration. Acute contact dermatitis of the face can resemble angioedema or erysipelas.

Management

The management of allergic contact dermatitis is not always easy because of overlapping irritant, allergic and endogenous factors. The *identification* of any offending allergen or irritant is the overriding objective. *Patch testing* (see below) will help in assessing the contribution of contact allergy and is particularly useful in dermatitis of the face, hands and feet.

Once the relevance has been demonstrated, the exclusion of an offending allergen from the environment is desirable and, if this can be achieved, the dermatitis may clear. The commonest allergens are nickel, fragrances, preservatives, para-phenylenediamine, rubber chemicals, colophonium and plants (Table 18.1). It may be difficult to eliminate fully all contact with ubiquitous allergens.

Allergen avoidance

Nickel sensitivity affects 10% of women and 1% of men. Usually, it causes only an inconvenient eczema at jewellery or metal contact sites, but an industrial dermatitis can result, e.g. in nickel platers or metal machinists.

Fragrances are ubiquitous in modern society and are present not only in cosmetics such as perfumes (Fig. 18.3) and deodorants (Fig. 18.4) but also in many household products. Similarly, *preservatives* are used in many products other than those for personal care. There has been an epidemic in Europe of contact allergy to the preservative methylisothiazolinone, which is found in cosmetics (including soaps

Specific HLA alleles are likely to be relevant to contact allergens, but no strong associations have been identified. Nickel hypersensitivity requires direct activation of the innate immune receptor TLR4 by nickel ions. It is unclear whether allergic contact dermatitis is more common in people with atopic eczema, but filaggrin gene mutations are associated with an increased risk of nickel allergy.

Induction of an allergic response (Fig. e18.1) is initiated through the skin. Chemical antigen is bound to self-proteins on, and processed by, skin dendritic cells, which migrate it to the draining lymph node for presentation to naive CD4+ T lymphocytes. With the correct co-stimulatory signals, T cell receptor ligation to the cutaneous dendritic cell major histocompatibility complex loaded with the self-protein: chemical allergen complex will induce proliferation and activation of the CD4+ cells. Within 5–7 days or longer, these specific effector T cells leave the lymph node and return to the skin under skin-homing molecular control where, when the chemical allergen is re-encountered, inflammation is induced producing dermatitis.

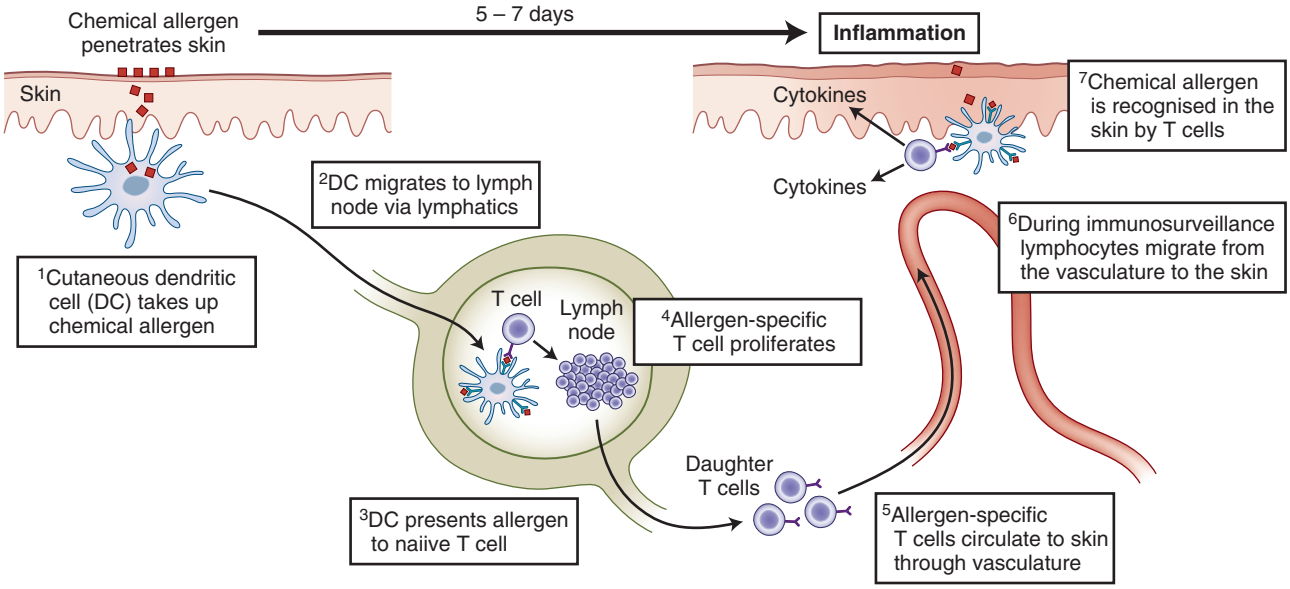


Fig. e18.1 The immunological mechanisms involved in the induction of allergic contact dermatitis.

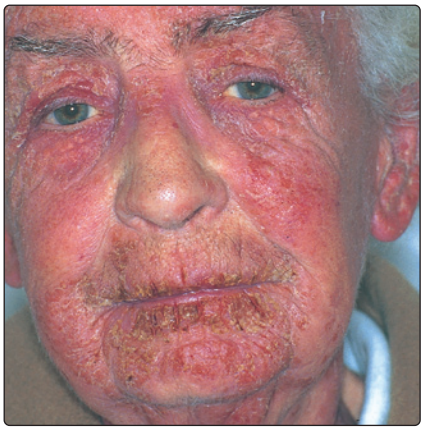


Fig. e18.2 Severe allergic contact dermatitis due to the use of a topical medicament that contained a constituent to which the patient was allergic. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

and shampoos) and in workplace products such as paints and cutting oils.

Rubber chemicals (such as thiurams) in rubber gloves are also common allergens (latex contact urticaria must be considered when a patient has reacted to rubber). Plants both domestic and as used in agriculture can also cause allergic (and irritant) contact dermatitis. *Poison ivy dermatitis* (contact allergy to the plant chemical urushiol) is a major problem in the United States.

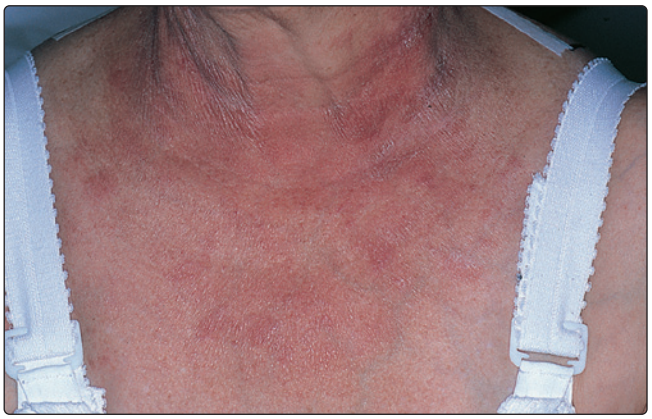


Fig. 18.3 Allergic contact dermatitis on the neck due to fragrances.

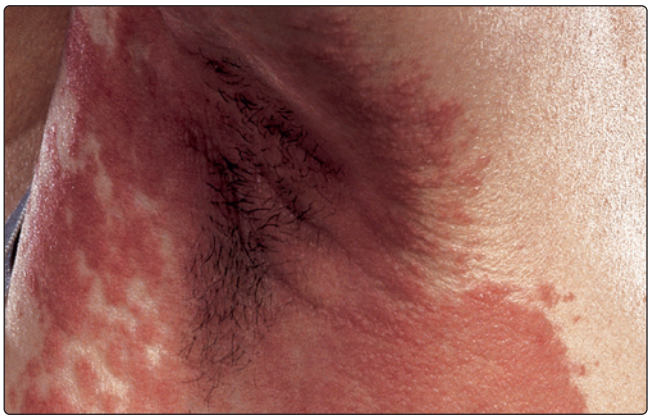


Fig. 18.4 Allergic contact dermatitis at the axilla due to a component of a roll-on deodorant.

Patch testing

The epicutaneous patch test detects *cell-mediated* (*type IV*) *hypersensitivity* (p. 10). It is very helpful in the investigation of contact dermatitis. Commercially prepared allergens are available in the correct concentration for testing, usually in petrolatum (or sometimes water) as a diluent. Details of the procedure are shown in Fig. 18.5.

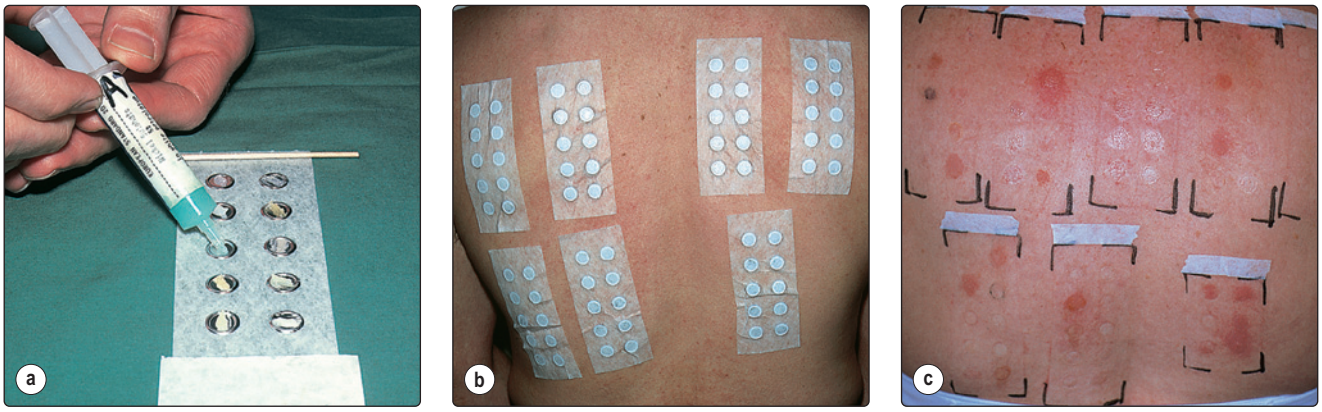


Fig. 18.5 Patch testing methodology.

(a) Patch tests are prepared.
Small amounts of the test substances are applied to the 8-mm-diameter aluminium discs on adhesive tape (Finn chambers) that are used for patch testing. The exact selection of test substances depends on taking a detailed history including the clinical problem, the site of the dermatitis, the environmental contacts (noting ingredients labels on any cosmetics or workplace products used) and the patient's occupation.

(b) Patch tests are applied.
A 'standard series' of 41 substances is applied to every patient, with additional allergens as necessary. A record sheet is kept. The patches are fixed to the upper back, left on for 2 days and then removed after marking the top margin of each text strip with adhesive tape or with a marker pen.

(c) Patch tests are read.
Numerous allergic-positive patch test sites are shown. A positive allergic response is manifest by a localized eczema reaction, which is scored according to the following convention:

?+ doubtful: faint erythema only,
+ weak: erythema, maybe papules,
++ strong: vesicles, infiltration,
+++ extreme: bullous,
IR irritant (of various types, but often showing a glazed circumscribed area, frequently with increased skin markings).

The test sites are read for a second time at 4 days, as positive reactions commonly do not appear until this time. The results are interpreted in the light of the clinical situation: a positive reaction is not always relevant to the current skin problem. Relevance can be demonstrated by showing prior exposure to a product containing the allergen to which the patient has had an allergic reaction. Common allergens and their sources are shown in Table 18.1.

Allergic contact dermatitis

- **Activation by an allergen of specifically-sensitized T cells** initiates a cascade of local inflammation that results in the clinical picture of allergic dermatitis.
- **Pointers towards the diagnosis of allergic contact dermatitis** include specific localization of an eczema and a history of potential allergen contact.
- **Irritant and endogenous factors often coexist** with allergic dermatitis.
- **Allergic contact dermatitis is usually localized to the site of allergen contact**, although secondary eczematous spread may occur.
- **Patch testing** is helpful to confirm allergic contact dermatitis, particularly of the face, hands and feet. Specific immunoglobulin (Ig) E tests or prick tests may also be needed, e.g. for latex.
- **Common allergens:** include nickel, rubber chemicals, fragrances, chromate, cobalt, colophonium, preservatives, plant allergens and para-phenylenediamine.
- **Elimination and avoidance** of an allergen, or its substitution, are useful, but prevention of initial sensitization is the ideal. Legislation may be needed to control exposure to some environmental allergens.

In the United States, allergic contact dermatitis to poison ivy is a particular problem because it produces an excessive reaction in those who are exposed to the plant, which is widely distributed across the North American continent. The eruption is often an acute dermatitis with blisters (Fig. e18.3).

Chromate allergy typically causes a chronic hand dermatitis in bricklayers but may also cause a shoe or hand dermatitis from leather, as chromate is used in the tanning of leather (Fig. e18.4).

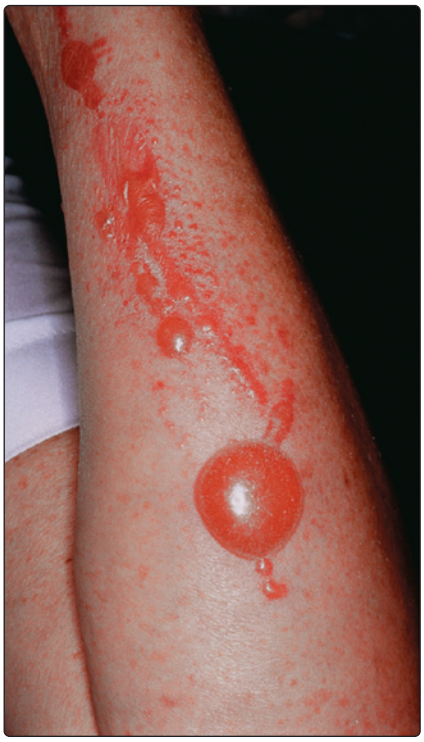


Fig. e18.3 Acute allergic contact dermatitis in poison ivy dermatitis. Large blisters reflect the severity of the reaction. The streaky linear blisters indicate the stroking of the plant along the arm and are seen, usually to a lesser degree, in other cases of plant dermatitis.

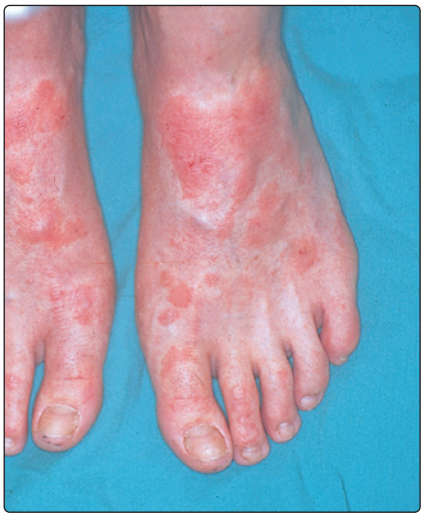


Fig. e18.4 Allergic contact dermatitis to shoes. An acute dermatitis with papules and small vesicles is evident. The distribution suggests a shoe dermatitis. Patch testing showed an allergic positive reaction to chromate. Leather tanned using a vegetable dye is an alternative to chromate tanning.

A 'standard series' of 41 substances is applied to every patient, with additional allergens as necessary (details can be found on the website of the British Society for Cutaneous Allergy, access via http://www.cutaneousallergy.org/). A record sheet is kept. The patches are fixed to the upper back, left on for 2 days and then removed after marking the top margin of each text strip with adhesive tape or with a marker pen.

Further reading – online sources

More information is available at the website of the British Society for Cutaneous Allergy (access via http://www.cutaneousallergy.org/), from which patient information sheets also may be downloaded.

Further reading – textbooks

Readers are referred to specialized texts such as:

Chew, A.-L., Maibach, H.I. (Eds.), 2006. Irritant Dermatitis. Springer, Berlin.

Johansen, J.D., Frosch, P.J., Lepoittevin, J.P. (Eds.), 2011. Contact Dermatitis, 5th ed. Springer, Berlin.

19 | Eczema – Atopic eczema

Definition

Atopic eczema is predominantly a disease of childhood that gives rise to poorly demarcated chronic pruritic papular inflammation of the skin. Uncontrollable scratching is prominent. Most cases improve with age, although approximately 50% of children retain evidence of the condition into adult life. For diagnostic criteria, see Box 19.1. 'Atopy' defines those with an inherited tendency to develop asthma, allergic rhinitis, conjunctivitis or atopic eczema and is present in 15–25% of the population. Atopics produce high levels of circulating immunoglobulin (Ig)E antibodies, commonly to inhalant allergens (e.g. house-dust mite). Confusingly, not all those with the clinical pattern of 'atopic eczema' show raised IgE, therefore the diagnostic criteria do not include measurements of IgE.

Box 19.1 Diagnostic criteria for atopic dermatitis

Evidence of itchy skin or parental report of scratching or rubbing, plus three or more of the following:

- History of involvement of the skin creases
- History of asthma or hay fever (or first-degree relative if under 4 years of age)
- History of generally dry skin in the past year
- Onset under 2 years old (not used if child is under 4 years)
- Visible rash on the flexures (including face if under 4 years).

(Adapted from Williams HC, Burney PG, Pembroke AC, Hay RJ. 1994. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. Br J Dermatol 131(3):406–416.)

Aetiopathogenesis

Skin barrier

Individuals with atopic eczema have an impaired skin barrier, which allows excess water loss through the skin (drying effect) and an increased potential for exogenous irritants and allergens to penetrate (inducing inflammation). Discovery of a strong association between loss-of-function mutations in the gene encoding filaggrin, which is a skin barrier protein expressed in the outer layers of the epidermis, and individuals with atopic eczema has shown how critical epidermal function is to development of atopic eczema.

Immunology

Individuals with atopic eczema make aberrant immune responses to environmental allergens, which become skewed towards Th2 responses (p. 10), inducing allergen-specific IgE production. The basic cause of these immune defects is still unclear. However, the serum IgE is normal in 20% of atopic eczema subjects.

Incidence

About 20–30% of UK infants are affected. The condition usually starts within the first 6 months of life and, by 1 year, 60% of those likely to develop atopic eczema will have done so. Two-thirds have a family history of atopy. Remission occurs within 10–20 years in 40–60%, although some relapse later.

Clinical presentation

The appearance of atopic eczema differs depending on the age of the patient.

Infancy

Babies develop an itchy vesicular exudative eczema on the face (Fig. 19.1), head and hands, often with secondary infection. About half continue to have eczema beyond 18 months.

Childhood

After 18 months, the pattern often changes to the familiar involvement of the flexures (antecubital and popliteal fossae, neck, wrists and ankles) (Figs 19.2 and 19.3). The face often shows erythema and infraorbital folds. Lichenification, excoriations and dry skin (Fig. 19.4) are common, and palmar markings may be increased. Post-inflammatory hyperpigmentation occurs in those with dark skin. Scratching and rubbing cause most of the clinical signs and are a particular problem at night when they can interfere with sleep. Behavioural difficulties can occur, and a child's eczema can disrupt family life. Occasionally, a 'reverse pattern' of eczema is seen, with involvement of the extensor aspects of the knees and elbows.

Adults

The commonest manifestation in adult life is hand dermatitis, exacerbated by irritants, in someone with a past history of atopic eczema. However, a small number of adults have a chronic severe form of generalized and lichenified atopic eczema (Fig. 19.5), which may interfere

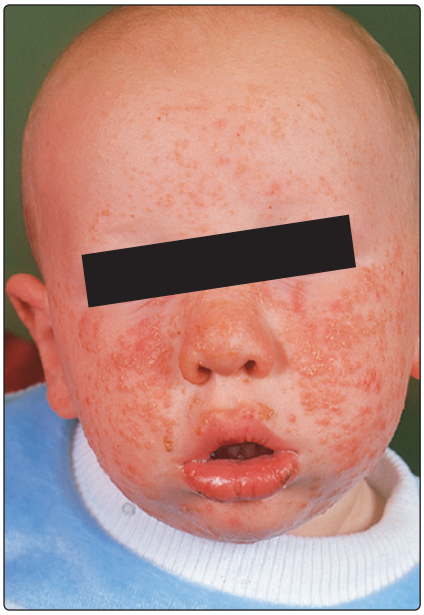


Fig. 19.1 Atopic eczema in an infant. Secondary bacterial infection was present.

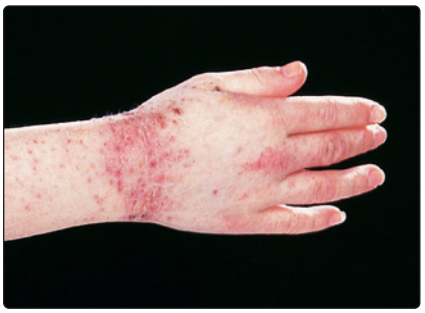


Fig. 19.2 Atopic eczema in a child, showing excoriations and lichenification at the wrist.

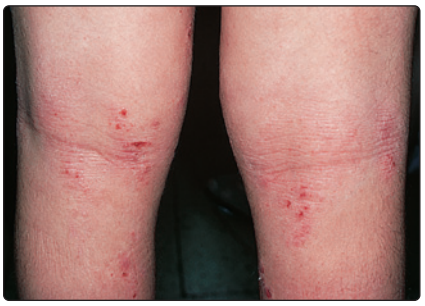


Fig. 19.3 Atopic eczema involving the popliteal fossa in a child.

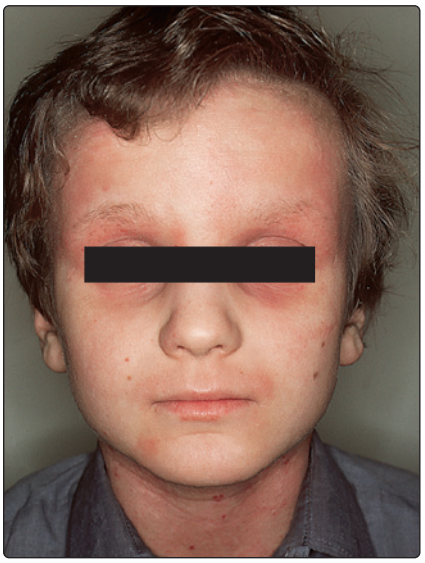


Fig. 19.4 A 'dry' pruritic type of atopic eczema. Note the loss of eyebrows due to constant rubbing of the face.

Individuals with atopic eczema have an impaired skin barrier, which allows excess water loss through the skin (drying effect) and an increased potential for exogenous irritants and allergens to penetrate (inducing inflammation). Discovery of a strong association between loss-of-function mutations in the gene encoding filaggrin, which is a skin barrier protein expressed in the outer layers of the epidermis, and individuals with atopic eczema has shown how critical epidermal function is to development of atopic eczema (Fig. e19.1).

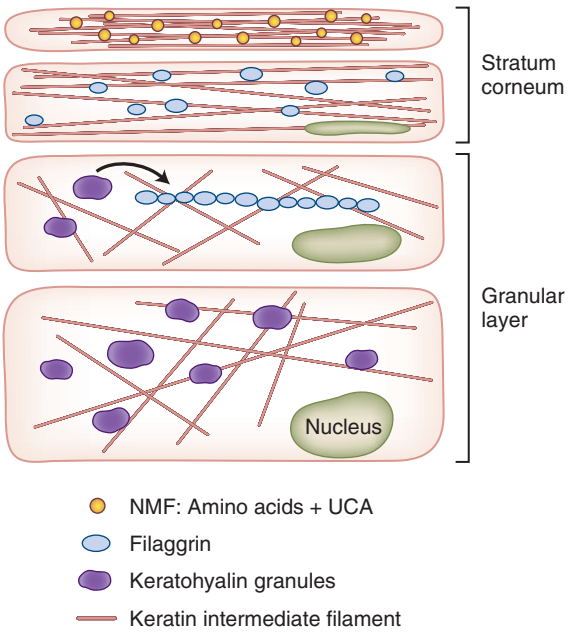


Fig. e19.1 Keratohyalin granules are synthesized in keratinocytes in late differentiation in the outer epidermis, which denotes the granular cell layer.

Degradation of keratohyalin granules into the component chains of pro-filaggrin is followed by further processing to filaggrin monomers. These proteins are important for adherence between keratin intermediate filaments, which maintain the cytoskeleton during further differentiation. As the keratinocyte loses viability, the nucleus collapses and organelles are lost. Corneocytes comprise the outer epidermis and are important in formation of the stratum corneum. Filaggrin monomers undergo proteolysis to amino acids and urocanic acid ('natural moisturizing factor'), which acts in a hygroscopic manner to retain water in the epidermis. Individuals with mutations in the filaggrin gene have less filaggrin in their skin, and show an increased risk of atopic eczema, which is thought to be mediated by the subsequent defect in the skin barrier.

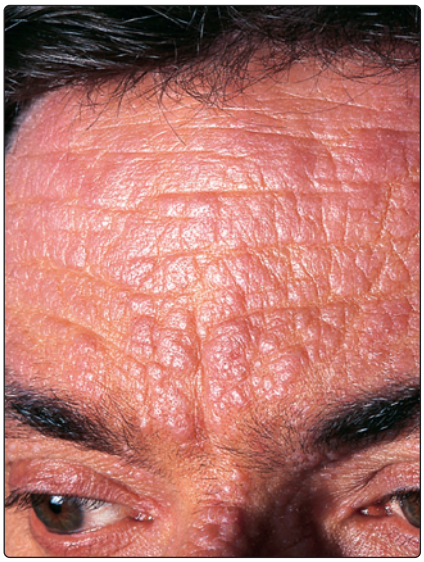


Fig. 19.5 Grossly lichenified and nodular atopic eczema on the face of an adult.

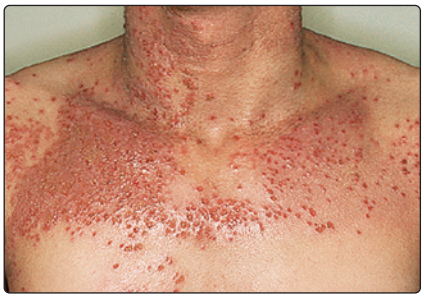


Fig. 19.6 Eczema herpeticum. Herpes simplex infection complicating atopic eczema.

with their employment and social activities. Stressful situations, such as examinations or marital problems, often coincide with exacerbations.

Differential diagnosis

Scabies should be excluded. The differential diagnosis of atopic dermatitis includes underlying immunodeficiency (p. 59). Investigations are generally not required but may be useful in some situations (p. 36).

Patch testing is important in those who fail to respond to standard therapies or those with warning signs of allergic contact dermatitis (e.g. clear demarcation of eczema, hand or facial eczema) (p. 36).

Complications

- *Bacterial infection*. Most individuals with atopic eczema are colonized with *Staphylococcus aureus* (p. 51) and invasive infection is a common cause of disease exacerbations.
- *Viral infection* including *eczema herpeticum*. There is a propensity to develop widespread herpes simplex (Fig. 19.6). Patients also have an increased susceptibility to infection with molluscum contagiosum.
- *Yeast infection*. Overgrowth of *Malassezia furfur* is common and some individuals respond to treatment with topical or oral imidazoles.
- *Cataracts*. A specific form of cataract infrequently develops in young adults with severe atopic eczema.
- *Growth retardation*. Children with severe atopic eczema may have short stature. Topical steroid therapy is unlikely to be causal.

Management

General measures include explaining the disorder and its treatment to the patient and the parents, stressing the normally good prognosis. Nails should be kept short. The exclusion of house-dust mite from the home environment is difficult. Career advice to avoid wet work jobs (e.g. nursing, hairdressing, cleaning) and those with exposure to irritant oils is important. Some sufferers obtain support from groups such as the National Eczema Society.

Specific treatments for atopic eczema are summarized in Table 19.1.

Topical therapy

Washing and emollient therapy

Emollients (p. 22) are the most important treatment, a variety should be offered to increase compliance, and time should be spent explaining how to apply them. They moisturize the dry skin, diminishing the desire to scratch and reducing the need for topical steroids. The greasy emollients (ointments) are more effective at repairing the skin barrier and therefore are usually more effective. Creams containing antiseptics such as chlorhexidine and bath oils may also help. Emollients should be used regularly on the skin and to wash with. Soap and 'bubbly' products should be completely avoided.

Topical steroids and calcineurin inhibitors

In children, 1% hydrocortisone ointment applied once a day is usually adequate (ointments are generally preferred to creams for eczema). Moderate potency steroid may be used for a short time in children with resistant eczema, and for more prolonged periods in adults. Steroids in conjunction with topical antibiotics may be of help in infected eczema. Tacrolimus ointment (0.03% children, 0.1% adults) or pimecrolimus are alternatives to steroids, especially in facial and hand eczema.

Table 19.1 **Treatment for atopic eczema**

Treatment	Indication
Emollients	Most eczema; ichthyosis
Topical steroids	Most types of eczema
Topical tacrolimus	Steroid-resistant eczema
Tar bandage	Lichenified/excoriated eczema
Oral antihistamine	Pruritus
Oral antibiotic	Bacterial superinfection
Exclusion diet	Food allergy/resistant eczema
UVB, methotrexate, ciclosporin, mycophenolate and azathioprine	Resistant and severe eczema unresponsive to topical therapy

Therapeutic bandaging/clothing

Coal tar or ichthammol paste bandages normally left on overnight are useful for lichenified or excoriated eczema. Wet wraps or dry wraps are often required for a short time on an exudative eczema. Elasticated or silk impregnated clothing are often well tolerated and useful in children. Wool clothing irritates and should be avoided.

Systemic therapy

Sedative antihistamines, given at night, are helpful principally through the sedative effect. Infected exacerbations frequently require the intermittent use of an oral antistaphylococcal antibiotic. *Eczema herpeticum* should be assessed urgently and treated with aciclovir. Patients with severe and resistant forms of atopic eczema may be treated with narrow-band UVB (p. 112), methotrexate, azathioprine, mycophenolate mofetil or ciclosporin (p. 22). Novel therapies are on the horizon, including anti-IL4RA biologic therapy, which show great promise.

Dietary manipulation

Symptoms such as urticaria or angioedema following ingestion of food should be investigated by a specialist with an interest in allergy, but routine testing for specific IgE does not reliably predict those foods that may exacerbate eczema. Eczema around the mouth or perianal region, gastrointestinal symptoms and failure to thrive are suggestive of food allergy relevant to eczema. Dietician-supervised exclusion diets are reserved for a minority who have not improved with standard therapy.

Atopic eczema

- Affects 20–30% of UK infants: onset at less than 1 year in 60% of cases.
- Loss of skin barrier function, including filaggrin mutations is central to the disease pathogenesis.
- Classically affects the face in infants, later knee and elbow flexures.
- Itch–scratch cycle induces lichenification.
- Exacerbations are often due to infection, particularly staphylococcal.
- Treatment involves emollients, topical steroids, tacrolimus, clothing, systemic antihistamines and antibiotics.

20 Eczema – Other forms

The other main types of dermatitis are seborrhoeic, hand, pompholyx, discoid, venous and asteatotic eczema (Table e17.1).

Seborrhoeic dermatitis

Seborrhoeic dermatitis is a scaly eruption, usually affecting the scalp and eyebrows. Other patterns are recognized. The condition is usually less itchy than atopic eczema, but sometimes clinical distinction of these entities is difficult. Treatment is with mild topical corticosteroids and anti-yeast therapy (Ch. 31).

Hand dermatitis

Hand dermatitis is a common, often recurrent condition that varies from being acute and vesicular to chronic, hyperkeratotic and fissured. The condition results from a variety of causes, and several factors are often involved. In children, hand dermatitis is mostly due to atopic eczema. An atopic predisposition often underlies adult hand dermatitis, especially if caused by repeated exposure to irritants.

Allergic causes need excluding, and most adults with hand dermatitis require patch testing (Ch. 18). Fungal infection is ruled out by microscopy and culture, especially in unilateral hand dermatitis, and the feet are examined because tinea pedis can provoke a hand dermatitis as an 'id' phenomenon. A core of patients are left who have an endogenous recurrent hand dermatitis often characterized by sago-like vesicles on the sides of the fingers, on the palms and sometimes on the soles.

Box 20.1 Hints on hand care for patients with hand dermatitis

Hand washing

Use warm water and unscented soap; avoid paper towels and hot air dryers; instead use a dry cotton towel.

Protection

Avoid wet work if possible or wear cotton gloves under vinyl or nitrile gloves; wear gloves in cold weather and for dusty work.

Medicaments

Use emollients regularly throughout the day; apply steroid ointments twice a day.

Avoid handling

Shampoos, hair preparations, detergents, solvents, polishes, certain vegetables (e.g. tomatoes, potatoes), peeling fruits (e.g. oranges) and cutting raw meat.

Clinical presentation

Hand dermatitis often presents as a chronic eczema, but may appear as a vesicular eruption known as *pompholyx eczema* (see below). Vesicles may be seen with atopic eczema or contact dermatitis but, in pompholyx, there is usually no associated disorder.

Management

Most hand eczema is at least partially irritant, so reducing irritant exposures (e.g. soaps, detergents and wet work) and emollient use is always necessary. Advice for patients with hand dermatitis is given in Box 20.1. Hand PUVA may be appropriate in selected cases resistant to topical therapy. Alitretinoin (p. 23) has recently been licensed for severe chronic hand eczema refractory to potent topical corticosteroids.

Pompholyx eczema (cheiropompholyx)

Pompholyx eczema is an intensely itchy eruption on the hands and or feet, often in association with atopic eczema (Fig. 20.1).

Clinical presentation

The patient complaint of a recurrent eruption of 'pin-prick blisters on the sides of the fingers' associated with intense itch, subsequently leading to scaling and intermittent fissuring is so characteristic, that it is almost always a description of pompholyx eczema. Pompholyx eczema is diagnosed by the identification of small vesicles, which occasionally coalesce into bullae, located on the hands and/or feet, most commonly on the lateral aspects of the fingers. Itching is intense and excoriation leads to further inflammation. As the vesicles migrate upwards through the epidermis over weeks, they resolve with scaling over 1–2 weeks. A mild hyperkeratosis is common in the affected area, which may fissure on flexion of the skin. Unusually, this condition is frequently cyclical and often recurs on a monthly basis. Severe variants are not uncommon. The onset is in young adults, particularly in warm weather, and it is often recurrent. The association with hyperhidrosis has long been recognized and some individuals benefit from anti-hydrotic approaches. Involvement can be confined to a few microvesicles on the fingers, or it can be extensive with bullae affecting the whole hand. Some of these patients are nickel sensitive.

Management

Acute pompholyx requires drainage of large blisters and the application (once or twice a day) of wet dressings (e.g. immersed in 0.01% aqueous potassium permanganate or Burow's solution of 0.65% aqueous aluminium acetate). Oral antibiotics are given if bacterial infection is

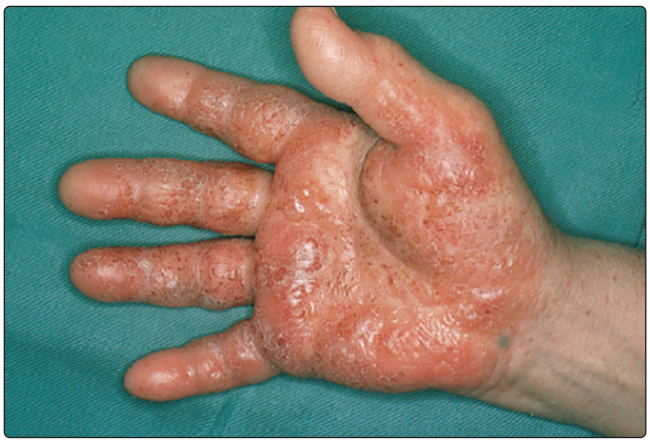


Fig. 20.1 Acute pompholyx involving the entire palmar surface of the hand in a nickel-sensitive woman.

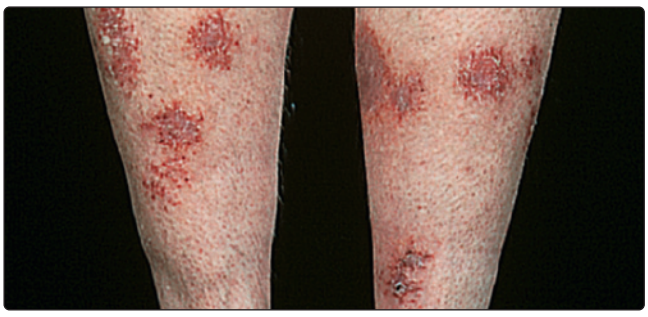


Fig. 20.2 Discoid eczema of the lower leg.

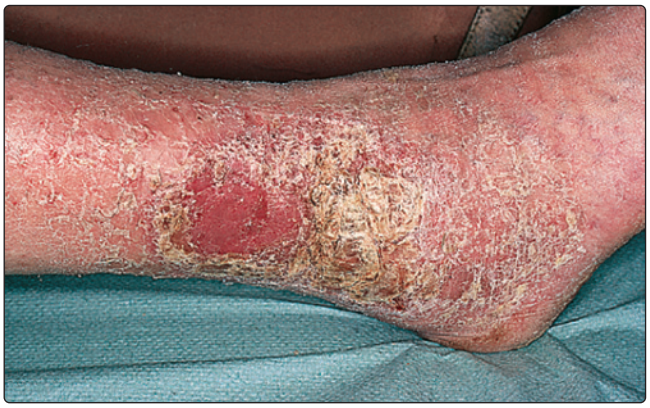


Fig. 20.3 Venous eczema.

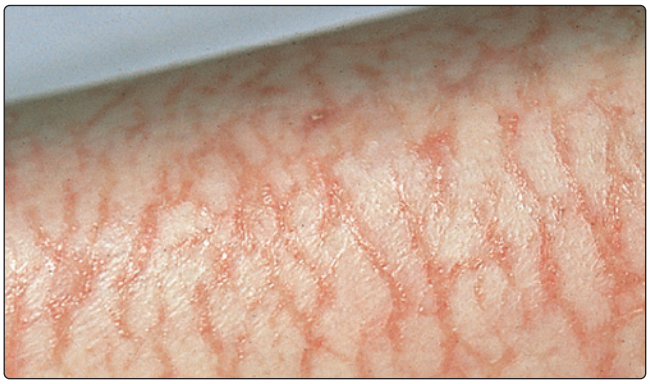


Fig. 20.4 Asteatotic eczema.

present. Some dermatologists prescribe systemic steroids, but these are usually not necessary. Once the acute stage settles, potent or highly potent steroid lotions or creams are used with cotton gloves. For chronic or subacute cases, a steroid ointment and emollients are helpful.

Discoid (nummular) eczema

Discoid eczema is an eczema of unknown aetiology characterized by coin-shaped lesions on the limbs; it typically affects middle-aged or elderly men (Fig. 20.2). Younger subjects, especially in dark skin types, may have atopic eczema.

Clinical presentation

The coin-shaped eczema lesions are often symmetrical and can be intensely itchy. The eczema may be vesicular or chronic and lichenified. It may clear after a few weeks, but tends to recur. Secondary bacterial infection is common.

Management

The condition can often be confused with tinea corporis and contact dermatitis. A potent or very potent topical steroid, often combined with an antimicrobial or antibiotic, is helpful.

Venous (stasis) eczema

Venous eczema affects the lower legs (Fig. 20.3) and is associated with underlying venous disease (p. 76). Incompetence of the deep perforating veins increases hydrostatic pressure in dermal capillaries. Pericapillary fibrin deposition impedes oxygen diffusion and leads to clinical changes.

Clinical presentation

Most patients are middle-aged or older women. Leashes of venules and haemosiderin pigmentation around the ankles are early signs. Eczema develops, sometimes with fibrosis of the dermis and subcutaneous tissue (lipodermatosclerosis) and ulceration. Contact allergy to an applied medicament can complicate the picture.

Management

An emollient, alone or with a mild or moderately potent steroid ointment, is needed. Tar-impregnated bandages applied once or twice a week are useful, especially when ulceration coexists. Venous disease or ulceration is treated on its own merit (p. 76).

Asteatotic eczema (eczema craquelé)

Asteatotic eczema is a dry eczema with fissuring and cracking of the skin, often affecting the limbs in the elderly (Fig. 20.4).

Overwashing of patients in institutions, a dry winter climate, hypothyroidism and the use of diuretics can contribute to eczema in the atrophic skin of old people. The skin of the limbs and trunk is erythematous, dry and itchy and shows a fine crazy-paving pattern of fissuring. Emollients applied to the skin and used in the bath often suffice to clear up the condition, but sometimes a mild steroid is necessary.

Other eczemas

Other types of eczema are occasionally encountered. They include: lichen simplex chronicus, lichen striatus, juvenile plantar dermatosis (p. 120) and napkin (diaper) eruption (p. 120).

Lichen simplex chronicus (neurodermatitis)

Neurodermatitis is an area of lichenified eczema due to repeated rubbing or scratching, as a habit or due to 'stress'. It usually occurs as a single plaque on the lower leg, back of the neck or in the perineum (*pruritus vulvae/ani*: p. 127). The skin markings are exaggerated, and pigmentation may occur. Asian and Chinese people are particularly susceptible. Sometimes a nodular lichenification known as *prurigo nodularis* develops on the shins and forearms. Emollients, topical steroids, weak tar-paste and tar-impregnated bandages are the mainstay of treatment.

Lichen striatus

Lichen striatus is a rare self-limiting linear eczema affecting a limb and occurring in adolescents (Fig. 9.3).

Eczema

- **Seborrhoeic dermatitis** commonly affects the scalp and face. It responds to combined antimicrobial/hydrocortisone creams.
- **Hand dermatitis:** multiple and mixed aetiology; determine causes by exclusion.
- **Pompholyx eczema:** characterized by recurrent micro-vesicles on the lateral fingers.
- **Discoid eczema** often presents as coin-shaped lesions on limbs of the middle-aged or older person. It improves with moderate potency topical steroids.
- **Venous eczema** is associated with venous disease. It responds to emollients and low or moderate potency topical steroids.
- **Hand dermatitis:** multiple and mixed aetiology; determine causes by exclusion.
- **Asteatotic eczema:** the eczema craquelé of elderly skin. Treat with emollients or low potency topical steroids.
- **Lichen simplex chronicus:** an area of lichenified eczema induced by persistent scratching, often found on the posterior neck or lower leg.
- **Lichen striatus:** a rare linear eczema.

21 Lichenoid eruptions

Lichen planus and other disorders with a lichenoid appearance of shiny flat-topped papules are presented here.

Lichen planus

Lichen planus is a relatively common pruritic papular dermatosis involving the flexor surfaces, mucous membrane and genitalia.

The cause is unknown, but an immune pathogenesis for lichen planus is suspected as T cells infiltrate the skin, immunoglobulin M is found at the dermoepidermal junction, a lichenoid eruption is part of graft-versus-host disease (p. 87) and there is an association with some autoimmune diseases.

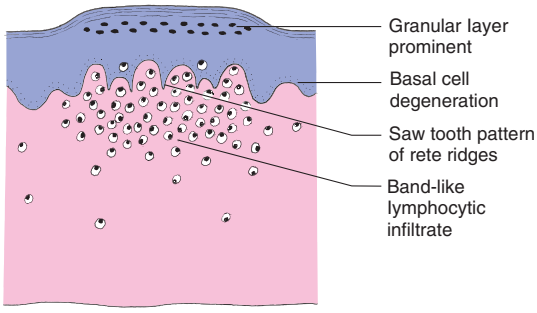


Fig. 21.1 Histopathology of lichen planus.

Pathology

In lichen planus, the granular layer is thickened, basal cells show liquefaction degeneration and lymphocytes infiltrate the upper dermis in a band-like fashion (Fig. 21.1).

Clinical presentation

Two-thirds of cases occur in the 30–60-year-old age group. It is uncommon at the extremes of age, and the sex incidence is equal. Lichen planus tends to start on the limbs. It may spread rapidly to become generalized within 4 weeks, but the commoner localized forms progress more slowly.

Typical lesions are very itchy, flat-topped polygonal papules, a few millimetres in diameter, which may show a surface network of delicate white lines (Wickham's striae). Initially, the papules are red, but they become violaceous (Fig. 21.2).

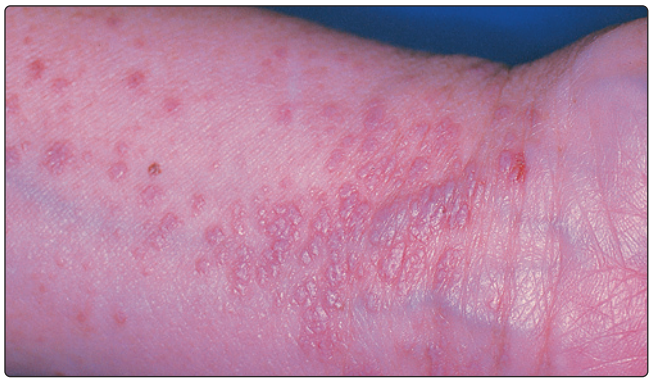


Fig. 21.2 Typical violaceous papules of lichen planus at the wrist.

The eruption is symmetrical and affects:

- the forearms and wrists
- the lower legs and thighs
- the genitalia, mucous membranes
- the palms and soles.

Mucous membrane involvement, especially of the buccal mucosa, occurs in up to two-thirds of cases, and may be present without skin lesions (Fig. 21.3). Lichen planus also shows the Koebner phenomenon (p. 19) which may explain some linear lesions. Follicular and other variants are found (see below). In most cases, papules flatten after a few months to leave pigmentation, but some become hypertrophic. Half of all patients are clear within 9 months, but 15% have continuing symptoms even after 18 months. Up to 20% have a further attack.

Lichen planus may be confused with other conditions, as shown in Table 21.1.

Variants of lichen planus

A number of variants of lichen planus exist:

- *Annular*. Found in 10% of cases, commonly on the glans penis.
- *Atrophic*. Rare, may be seen with hypertrophic lesions.
- *Bullous*. Blisters appear infrequently in lichen planus.
- *Follicular*. May occur with typical lichen planus; can affect the scalp alone (scarring alopecia; p. 71).
- *Hypertrophic*. Verrucous plaques affect the lower legs or arms (Fig. 21.4); may persist for years.
- *Mucous membrane*. Any mucosal surface may be affected, with or without lesions elsewhere. In the mouth, may represent contact allergy to mercury in amalgam fillings (see Fig. 21.3).

Complications

Lichen planus may be complicated by the following:

- *Nail involvement*. Found in 10% of patients. Longitudinal grooving and pitting are reversible, but dystrophic/atrophic lesions can produce scarring or permanent nail loss. Lichen planus affecting the nail can be severe and cause extensive nail damage.
- *Scalp lesions*. May be follicular, but pseudopelade-like permanent scarring alopecia is more common (p. 71).
- *Malignant change*. Very infrequent.

Table 21.1 **Differential diagnosis: lichen planus**

Type of lichen planus	Differential diagnosis
Generalized	Lichenoid drug eruption Guttate psoriasis Atypical pityriasis rosea
Genital	Psoriasis, scabies Lichen sclerosus
Hypertrophic	Lichen simplex

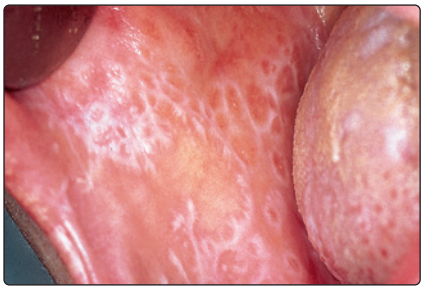


Fig. 21.3 White lace-like Wickham's striae on the buccal mucosa.

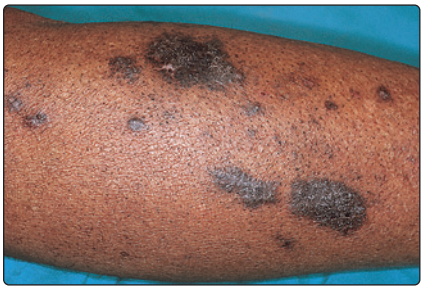
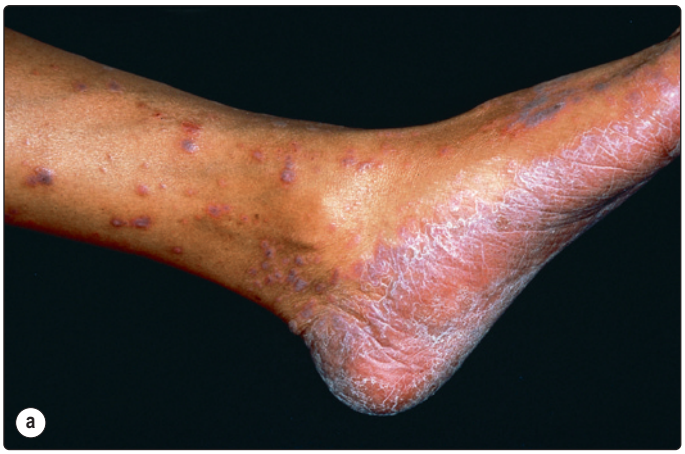


Fig. 21.4 Hypertrophic lichen planus showing hyperpigmentation.

Two-thirds of cases occur in the 30–60-year-old age group. It is uncommon at the extremes of age, and the sex incidence is equal. Lichen planus tends to start on the limbs (Fig. e21.1). It may spread rapidly to become generalized within 4 weeks, but the commoner localized forms progress more slowly. Typical lesions are very itchy, flat-topped polygonal papules, a few millimetres in diameter, which may show a surface network of delicate white lines (Wickham's striae). Initially, the papules are red, but they become violaceous (Fig. 21.2).

Mucous membrane involvement, especially of the buccal mucosa, occurs in up to two-thirds of cases, and may be present without skin lesions (Fig. 21.3 and Fig. e21.2). Lichen planus also shows the Koebner phenomenon (p. 19) which may explain some linear lesions. Follicular and other variants are found (see below). In most cases, papules flatten after a few months to leave pigmentation, but some become hypertrophic. Half of all patients are clear within 9 months, but 15% have continuing symptoms even after 18 months. Up to 20% have a further attack. Lichen planus may be confused with other conditions, as shown in Table 21.1.

- *Nail involvement*. Found in 10% of patients. Longitudinal grooving and pitting are reversible, but dystrophic/atrophic lesions can produce scarring or permanent nail loss. Lichen planus affecting the nail (Fig. e21.3) can be severe and cause extensive nail damage.



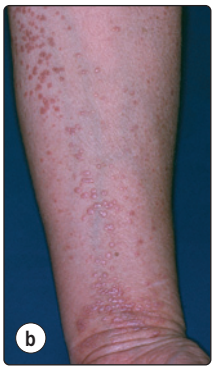


Fig. e21.1 (a) Lichen planus of the lower leg and sole of the foot. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)* **(b) Lichen planus of the forearm.** Numerous shiny papules are evident. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

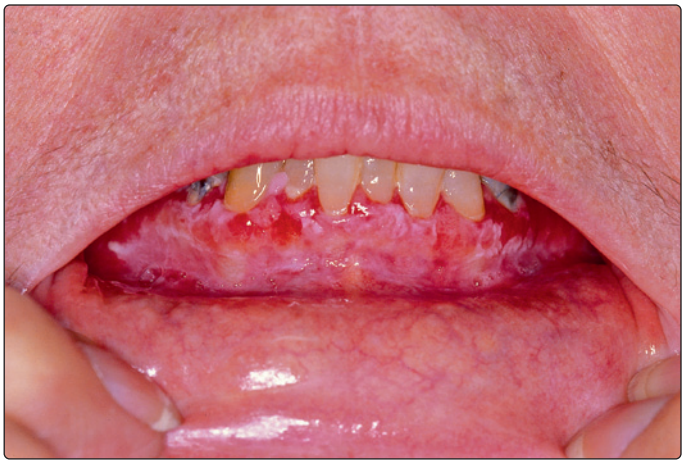


Fig. e21.2 Erosive lichen planus of the gingivae. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

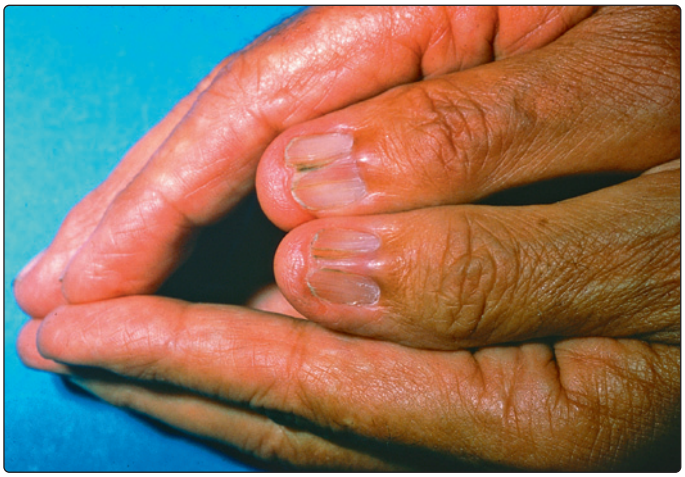


Fig. e21.3 Lichen planus of the thumbnails with the formation of a pterygium (a triangular fold of skin growing down over the nail plate). Lichen planus of the nails can be destructive and may warrant the use of a systemic corticosteroid. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Management

Lichen planus disease is self-limiting in most patients. Moderate to high potency topical steroids usually produce symptomatic improvement. Oral lesions are helped by a steroid-containing paste (e.g. triamcinolone acetone 0.1% dental paste) or topical tacrolimus. Hypertrophic lichen planus may require highly potent topical steroids, sometimes under occlusion, or intralesional steroid injection. Extensive involvement, ulcerative mucous membrane lesions or a potentially scarring nail dystrophy warrant a trial of oral prednisolone (in a dose of 10–20 mg/day) for 1–3 months. Long-term systemic steroids are not justified. Acitretin or psoralen with ultraviolet A (PUVA) may help resistant cases.

Lichen sclerosus

Lichen sclerosus is an uncommon disorder typified by white lichenoid atrophic lesions on the genitalia. Although associated with autoimmune disease, the cause is unknown.

Pathology

The epidermis may be thickened, thinned or hyperkeratotic. The upper dermis is oedematous with few cells; collagen is hyalinized. Lymphocytes infiltrate the lower dermis.

Clinical presentation

Lichen sclerosus occurs 10 times more frequently in women. It is commonest in middle age, although it may develop in childhood (with a better prognosis). Genital lesions are almost invariable, but involvement of the trunk or arms is seen. Individual lesions are a few millimetres in diameter, porcelain white and slightly atrophic, and may aggregate into wrinkled plaques (Fig. 21.5). Hyperkeratosis, telangiectasia, purpura and even blistering occur. Vulval and perianal lesions cause itching and soreness. Involvement in the male results in urethral stricture and phimosis (balanitis xerotica obliterans). Occasionally, lesions are found in the mouth. Lichen sclerosus is chronic and usually permanent in adults. Spontaneous resolution is most likely at puberty in childhood cases.

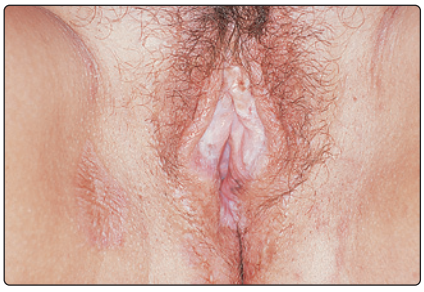


Fig. 21.5 Lichen sclerosus of the vulva.

Differential diagnosis

Female genital involvement may resemble lichen simplex chronicus (p. 41), Bowen's disease (p. 129) and extramammary Paget's disease. Male genital lesions mimic lichen planus, psoriasis and some rare inflammatory and premalignant forms of balanitis (p. 129).

Complications

Shrinkage of the vulva occurs, and dyspareunia is a problem in females. Males may experience recurrent balanitis and ulceration of the glans. Squamous cell carcinoma develops infrequently in the longstanding lesions of both sexes.

Management

Non-genital lesions require no treatment. In female genital involvement, a moderate or potent strength steroid cream will reduce the itch and prevent scarring. Vulvectomy is contraindicated in uncomplicated cases.

Treatment is similar for the male genital lesions, although circumcision is performed if phimosis develops. Both sexes need long-term follow-up and biopsy of any suspicious areas.

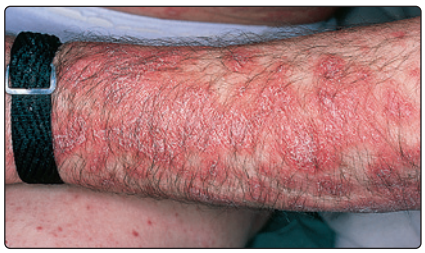


Fig. 21.6 A lichenoid drug eruption with psoriasiform features, here due to quinine.

Table 21.2 **Drugs causing a lichen planus-like eruption**

Type of agent	Drug
Antiarthritic	Gold, penicillamine, NSAIDs
Antidiabetic	Tolbutamide, chlorpropamide
Antiinfective	Ketoconazole, tetracyclines
Antihypertensive	Captopril, enalapril, beta-blockers, nifedipine
Antimalarial	Chloroquine, mepacrine, quinine
Antipsychotic	Phenothiazines, lithium
Antituberculous	Isoniazid, ethambutol, streptomycin
Biologics	Infliximab, etanercept, adalimumab
Diuretic	Thiazides, furosemide
New drugs	Imatinib, misoprostol
Statin	Simvastatin, pravastatin

Lichen nitidus

Lichen nitidus is an uncommon eruption of minute monomorphic flesh-coloured papules. The aetiology is unknown. Histology reveals a lymphohistiocytic infiltrate, which expands a single dermal papilla.

Clinical presentation and management

The eruption is asymptomatic, often noticed by chance, and usually occurs in children or young adults. Uniform pinhead-sized papules, which may be grouped, are seen on the forearms, penis, abdomen and buttocks. The main differential diagnosis is lichen planus (with which it may coexist) and keratosis pilaris (p. 94).

Treatment is usually unnecessary. Lichen nitidus may resolve in weeks or persist indefinitely.

Lichen planus-like drug eruption

An eruption resembling lichen planus can follow the ingestion of several drugs.

Clinical presentation

A lichen planus-like rash has been recognized with gold and mepacrine therapy for many years. The eruption, which can be severe, is often more 'psoriasiform' and hyperpigmented than true lichen planus (Fig. 21.6) and, on histology, shows a greater number of eosinophils. Resolution after withdrawal of the drug is often slow. Table 21.2 lists some of the drugs responsible.

Lichenoid eruptions

- **Lichen planus** is a relatively common pruritic papular eruption, which resolves in most cases within 18 months.
- **Lichen planus-like drug eruption** resembles lichen planus but is more persistent; it is seen, e.g. with gold, chloroquine and thiazides.
- **Lichen nitidus** is a rare, asymptomatic eruption of fine monomorphic papules on the abdomen, arms and penis.
- **Lichen sclerosus** is most common in women, and frequently affects the genitalia. Vulval shrinkage may occur. Topical steroids are helpful. There is a risk of malignant change.

The eruption is asymptomatic, often noticed by chance, and usually occurs in children or young adults. Uniform pinhead-sized papules, which may be grouped, are seen on the forearms, penis, abdomen and buttocks (Fig. e21.4). The main differential diagnosis is lichen planus (with which it may coexist) and keratosis pilaris (p. 94).

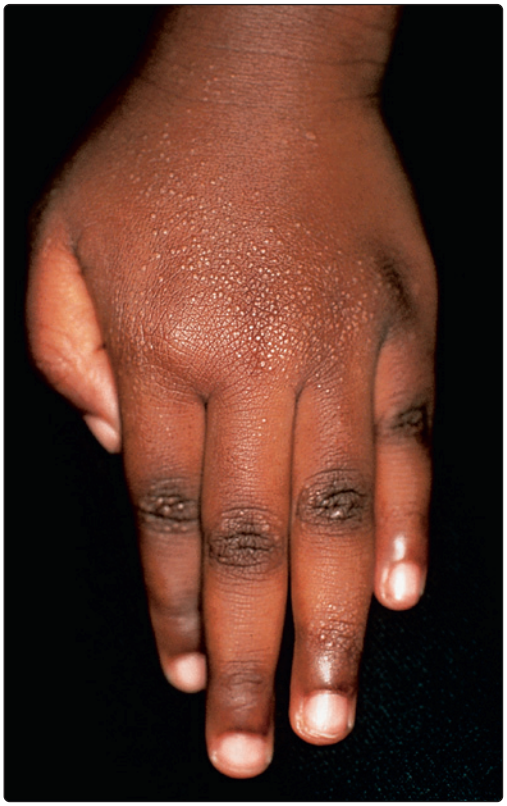


Fig. e21.4 Lichen nitidus. Numerous tiny flat-topped papules on the dorsal aspect of the hand. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Further reading – online sources

More information on the lichenoid eruptions can be found at the Medscape website (access via http://emedicine.medscape.com).

Further reading – textbooks

There are no current books dedicated to the lichenoid eruptions. Readers are referred to the standard texts:

Bolognia, J.L., Jorizzo, J.L., Schaffer, J.V. (Eds.), 2012. Dermatology, third ed. Elsevier Saunders, Philadelphia, PA.

Burns, T., Breathnach, S., Cox, N., et al. (Eds.), 2010. Textbook of Dermatology, eighth ed. Blackwell, Oxford.

22 Papulosquamous eruptions

Papulosquamous eruptions are raised, scaly and marginated, and include psoriasis, lichen planus and other conditions listed in Table 22.1. Eczema is not included as it does not usually have a sharp edge. These eruptions are not related aetiologically. Several are characterized by fine scaling and have the prefix 'pityriasis', which means 'bran-like scale'.

Table 22.1 Papulosquamous eruptions

Chronic superficial dermatitis
Drug eruption (p. 90)
Lichen planus (p. 42)
Pityriasis rubra pilaris (p. 46)
Pityriasis versicolor
Pityriasis alba
Pityriasis lichenoides
Pityriasis rosea
Psoriasis (p. 28)
Reiter's disease
Secondary syphilis
Tinea infection (p. 60)

Pityriasis rosea

Pityriasis rosea is an acute, self-limiting disorder probably infective in origin, characterized by scaly oval papules and plaques that occur mainly on the trunk.

Clinical presentation

The generalized eruption is preceded in most patients by the appearance of a single lesion, 2–5 cm in diameter, known as a 'herald patch' (Fig. 22.1). Some days later, many smaller plaques appear, mainly on the trunk but also on the upper arms and thighs. Individual plaques are oval, pink and have a delicate peripheral 'collarette' of scale. They are distributed parallel to the lines of the ribs, radiating away from the spine. Itching is mild or moderate. The eruption fades spontaneously in 4–8 weeks. It tends to affect teenagers and young adults. The cause is unknown, but epidemiological evidence of 'clustering' suggests an infective aetiology.

Differential diagnosis and management

Guttate psoriasis, pityriasis versicolor and secondary syphilis may cause confusion. A serological test for syphilis is needed in doubtful cases. The condition is self-limiting, and treatment does not hasten clearance, although a moderate potency topical steroid can help to relieve pruritus.

Pityriasis (tinea) versicolor

Pityriasis versicolor is a chronic, often asymptomatic, fungal infection characterized by pigmentary changes and involving the trunk. It is discussed in detail on page 62.

Reiter's disease

Reiter's disease is a syndrome of polyarthropathy, urethritis, iritis and a psoriasiform eruption.

Clinical presentation and management

Reiter's disease almost invariably affects males aged between 20 and 40 years, who have the HLA-B27 genotype and commonly follows a genitourinary or bowel infection. The joint and eye changes are often severe. Skin involvement includes a balanitis (p. 129) and red, scaly, pustular, psoriasiform plaques on the feet, known as 'keratoderma blennorrhagicum' (Fig. 22.2). Severe skin changes are unresponsive to topical therapy, and methotrexate or acitretin by mouth is often needed.

Pityriasis lichenoides

Pityriasis lichenoides occurs in children and young adults. There are two forms both of which are uncommon. Recent findings suggest pityriasis lichenoides may represent a T cell lymphoproliferative disease.

Clinical presentation

The acute form is characterized by an eruption of symmetrical oval or round pink-coloured macules and papules 2–3 mm in diameter that occur in crops sometimes over the whole body but often most pronounced on the trunk and the flexor aspects of the thighs and upper arms (Fig. 22.3). The papules often evolve in a polymorphic manner, through vesicular, necrotic and occasionally purpuric forms with a fine crust, and leave scars on healing. Rarely an acute febrile and ulcerating presentation is seen in young males, with systemic upset.

The chronic form occurs in a similar distribution to the acute variety. It is typified by firm lichenoid papules, 3–10 mm in diameter, that are reddish-brown in colour and topped by a characteristic 'mica' scale. These evolve over a month or so to leave brownish macules. The outlook is variable as new crops can keep appearing over a period of weeks. Most cases resolve within 6 months, though recurrences can occur.

Differential diagnosis

The acute form needs to be distinguished from varicella, vasculitis or lymphomatoid papulosis (p. 110.e1), the chronic type from guttate psoriasis and lichen planus.

Management

Phototherapy and topical steroids can provide symptomatic relief. The aggressive acute variant may require immunosuppressive drugs.

Chronic superficial dermatitis

Previously known as parapsoriasis, a term best avoided, this is an uncommon chronic dermatitis of small scaly pink–brown oval or round-shaped plaques,

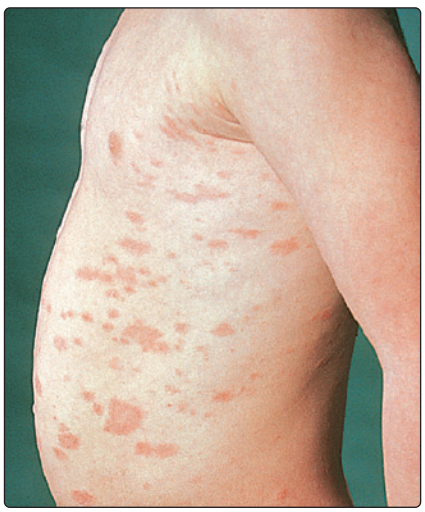


Fig. 22.1 Pityriasis rosea in a child, showing a herald patch on the lower abdomen and associated oval scaly plaques.

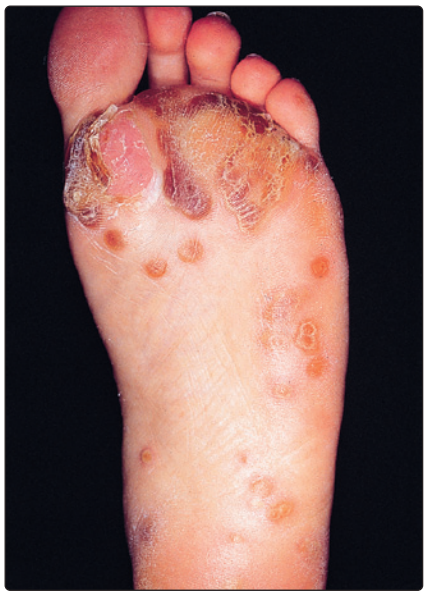


Fig. 22.2 Reiter's disease showing the features of keratoderma blennorrhagicum. *(From Callen JP, Jorizzo JL, Bolognia JL, Piette WW, Zone JJ 2003 Dermatological Signs of Internal Disease, 4th edition. Saunders, with permission.)*

The generalized eruption is preceded in most patients by the appearance of a single lesion, 2–5 cm in diameter, known as a 'herald patch' (Fig. 22.1 and Fig. e22.1). Some days later, many smaller plaques appear, mainly on the trunk but also on the upper arms and thighs. Individual plaques are oval, pink and have a delicate peripheral 'collarette' of scale. They are distributed parallel to the lines of the ribs, radiating away from the spine. Itching is mild or moderate. The eruption fades spontaneously in 4–8 weeks. It tends to affect teenagers and young adults. The cause is unknown, but epidemiological evidence of 'clustering' suggests an infective aetiology.

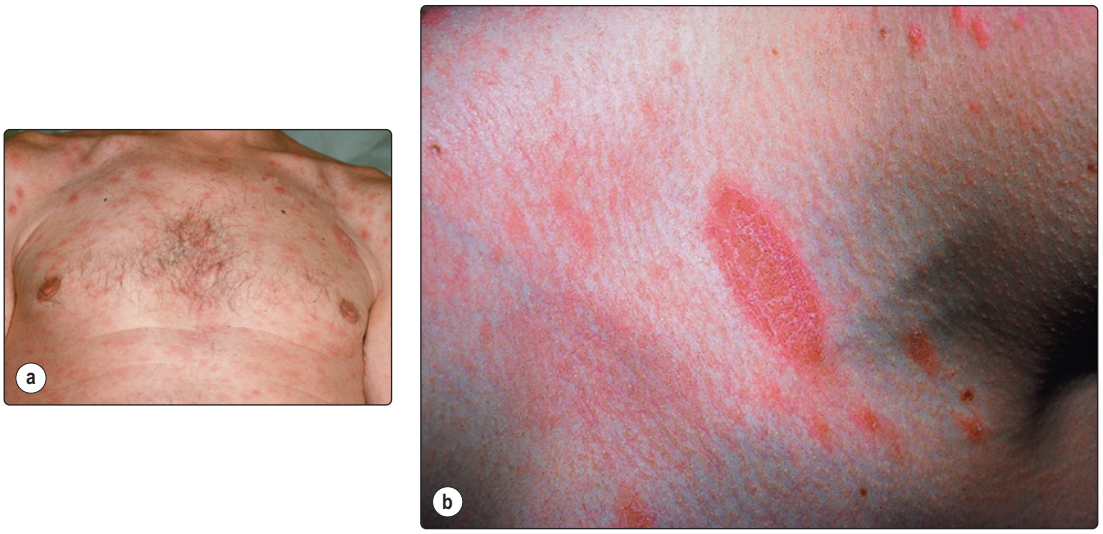


Fig. e22.1 Pityriasis rosea in an adult. (a) The patches are rather diffuse. The herald patch is located at the left shoulder. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)* **(b) The herald patch of pityriasis rosea on the right side of the neck in another patient.** *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

mainly on the trunk. The variant with larger plaques may proceed to mycosis fungoides (cutaneous T cell lymphoma) or be this from the onset.

Clinical presentation

In chronic superficial dermatitis, scaly patches develop, usually on the abdomen, buttocks or thighs (Fig. 22.4). The onset is in young to mid-adult life, and the plaques are indolent. It may be difficult to predict which cases will progress to mycosis fungoides (p. 110), especially as the evolution may take place over many years, but the 'benign' lesions tend to be small and finger-like in shape, whereas the 'premalignant' plaques are larger, asymmetrical, atrophic and can show associated poikiloderma (reticulate pigmentation, telangiectasia and atrophy). Biopsy is necessary to look for the changes of mycosis fungoides, and further biopsy of any changed area is required. The disease is often indolent and may persist over a period of several years.

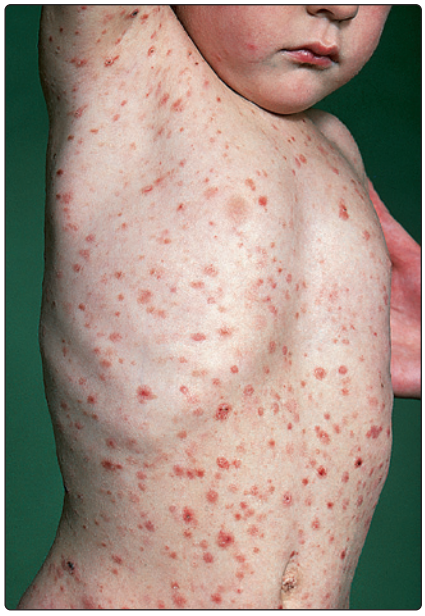


Fig. 22.3 Pityriasis lichenoides (acute type) in a child.

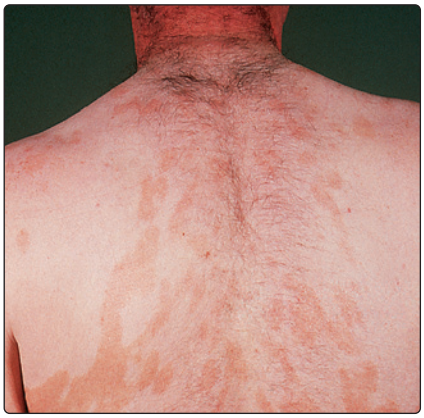


Fig. 22.4 Plaques of chronic superficial dermatitis on the back of a middle-aged man.

Differential diagnosis and management

Psoriasis, discoid eczema and tinea corporis may need to be considered in the diagnosis, but the plaques of chronic superficial dermatitis are distinguished by being fixed.

The first-line treatment with moderately potent topical steroids is sometimes helpful. Ultraviolet B (UVB) or psoralen with UVA (PUVA) will often be needed for the large plaque variant. Long-term follow-up is recommended.

Other pityriases

Other varieties of pityriasis include the following:

- *Pityriasis rubra pilaris*. A rare, scaly follicular eruption, which may progress to erythroderma (see p. 46).
- *Pityriasis alba*. Occurs in children or young adults and is characterized by fine scaly white patches on the face or arms. It is a type of eczema and often seen in atopic patients.

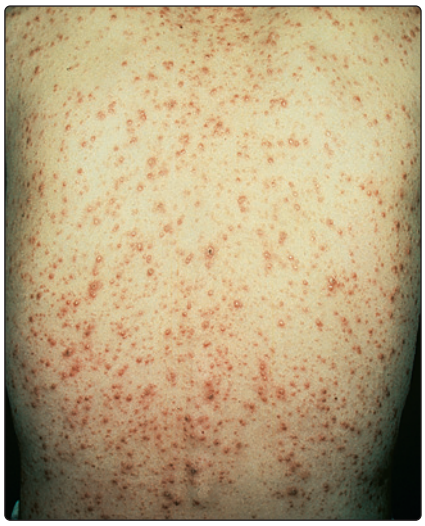


Fig. 22.5 Secondary syphilis. Coppery red-coloured macules and papules are evident on the trunk.

- *Pityriasis amiantacea*. Large thick white keratinous scales firmly adherent to hair shafts, sometimes seen in psoriasis or seborrhoeic dermatitis.

Secondary syphilis

Definition

Secondary syphilis is an inflammatory response in the skin and mucous membranes to the disseminated *Treponema pallidum* spirochaete. There has been a resurgence of syphilis in recent years.

Clinical presentation

The secondary phase of syphilis (p. 126) starts 4–12 weeks after the appearance of the primary chancre and consists of an eruption, lymphadenopathy and variable malaise. Pink or copper-coloured macules, which later develop into papules, appear in a symmetrical distribution on the trunk and limbs and are non-itchy (Fig. 22.5). Annular patterns are not uncommon, and involvement of the palms and soles is distinctive. Other signs are moist warty lesions (condyloma lata) in the anogenital area, buccal erosions that may be arcuate (snail-track ulcers) and a diffuse patchy alopecia. Mucosal lesions are infectious. Without treatment, the lesions of secondary syphilis resolve spontaneously in 1–3 months.

Differential diagnosis and management

Pityriasis rosea, psoriasis, drug eruption, infectious mononucleosis, rubella and measles may need to be considered. Treponemal serology is positive in all patients with secondary syphilis. Treatment is with intramuscular benzathine benzylpenicillin (p. 126). Patients with syphilis are best managed by physicians familiar with the treatment of genitourinary infections.

Papulosquamous eruptions

- **Pityriasis rosea** is a fairly common self-limiting eruption that involves the trunk of young adults. Scaly oval plaques follow a herald patch. It may be infective in origin.
- **Pityriasis versicolor** is a common truncal eruption of young adults and is due to *Malassezia*, a commensal yeast. It is often revealed in the summer as pale areas adjacent to tanned skin.
- **Reiter's syndrome** typically affects young males and follows a genitourinary or bowel infection. Keratotic skin lesions are seen with eye and joint changes.
- **Chronic superficial dermatitis** is an uncommon truncal eruption seen in young or middle-aged adults. The large plaque variant may represent early cutaneous T cell lymphoma.
- **Pityriasis lichenoides** is a rare chronic eruption of scaly-topped papules on the trunk and limbs. An acute form may scar.
- **Secondary syphilis** is a symmetrical, non-itchy truncal eruption with mucosal and palmar or plantar lesions, due to infection with *Treponema pallidum*.

Further reading – online sources

Additional information on pityriasis rosea and other diseases mentioned here can be found at the Medscape, DermnetNZ and nhs.uk websites (access via http://emedicine.medscape.com/, http://www.dermnetnz.org/ and http://www.nhs.uk/Conditions/).

Further reading – textbooks

There are no current books dedicated to the papulosquamous eruptions. Readers are referred to the standard advanced texts:

Bolognia, J.L., Jorizzo, J.L., Schaffer, J.V. (Eds.), 2012. Dermatology, third ed. Elsevier Saunders, Philadelphia, PA.

Burns, T., Breathnach, S., Cox, N., et al. (Eds.), 2010. Textbook of Dermatology, eighth ed. Blackwell, Oxford.

23 Erythroderma

Definition

Erythroderma or generalized exfoliative dermatitis defines any inflammatory dermatosis that involves all or nearly all the skin surface (sometimes stated as more than 90%). It is a secondary process and represents the generalized spread of a dermatosis or systemic disease throughout the skin.

Pathology

The duration and severity of the inflammatory process play a greater part in determining the histology than the underlying cause. In the acute eruption, oedema of the epidermis and dermis is prominent, and there is an inflammatory infiltrate. More chronic lesions show lengthened rete ridges and thickening of the epidermis. Abnormal lymphocytes may eventually be apparent in those cases resulting from lymphoma, and specific changes identified on biopsy of a typical lesion when psoriasis, ichthyosiform erythroderma or pityriasis rubra pilaris is the cause.

Clinical presentation

Erythroderma is an uncommon but important dermatological emergency, as the systemic effects are potentially fatal. It is twice as common in men and mainly affects the middle-aged and elderly. The condition often develops suddenly, particularly when associated with leukaemia or an eczema.

General symptoms and signs

A patchy erythema may rapidly spread to be universal within 12–48 h and be accompanied by pyrexia, malaise and shivering. Scaling appears 2–6 days later and, at this stage, the skin is hot, red, dry and obviously thickened. The patient experiences irritation and tightness of the skin and feels cold. The exfoliation of scales may be copious and continuous. Scalp and body hair is lost when erythroderma has been present for some weeks. The nails become thickened and may be shed. Pigmentary changes occur and, in those with a dark skin, hypopigmentation is seen. The picture is influenced by the patient's general condition and the underlying cause. The commonest causes of erythroderma are eczema, psoriasis and lymphoma (Table 23.1). Other dermatoses, including drug eruptions and pityriasis rubra pilaris, may also be implicated. Multiple skin biopsies may help in diagnosis.

Eczema

Atopic eczema may become erythrodermic at any age. Erythroderma from eczema is most common in the elderly, in whom the eczema may be unclassified. Itch is often intense.

Psoriasis

At first, the eruption resembles conventional psoriasis but, when the exfoliative stage is reached, these specific features are lost (Fig. 23.1). The withdrawal of potent topical steroids or of systemic steroids, or an intercurrent drug eruption, can precipitate erythrodermic psoriasis. Sterile pinhead-sized pustules sometimes develop, and the condition may progress to generalized pustular psoriasis (p. 29).

Table 23.1 **Causes of erythroderma and their relative frequencies**

Cause	Frequency (%)
Eczema (contact/atopic/seborrhoeic/unclassified)	40
Psoriasis	25
Lymphoma/leukaemia/Sézary syndrome	15
Drug eruption	10
Pityriasis rubra pilaris/ichthyosiform erythroderma	1
Other skin disease	1
Unknown	8

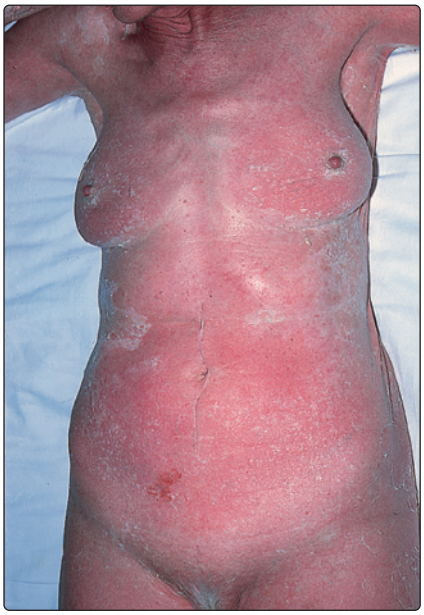


Fig. 23.1 Erythrodermic psoriasis.

Lymphoma/Sézary syndrome

Early biopsies may not be specific, and this may delay diagnosis, although universal erythroderma, infiltration of the skin and severe pruritus are helpful pointers (p. 110). Lymphadenopathy is often prominent, but the nodes are not always involved by lymphoma. Sézary syndrome (Fig. 23.2) typically occurs in elderly males and is characterized by the presence of abnormal T lymphocytes with large convoluted nuclei (Sézary cells) in the blood and skin. Patients may be stable for a number of years, then deteriorate rapidly.

Drug eruption

An acute drug eruption (p. 90), often of the drug hypersensitivity syndrome type, may become erythrodermic (Fig. 23.3). Carbamazepine, phenytoin, diltiazem, cimetidine, gold, allopurinol and sulphonamides are the commonest culprits.

Pityriasis rubra pilaris

Pityriasis rubra pilaris (PRP) is a disorder of unknown aetiology that begins in adults with redness and scaling of the scalp and progresses to cover the limbs and trunk (Fig. 23.4). It is a follicle-based eruption and characteristically shows islands of sparing and a yellow keratotic thickening of the palms (Fig. 23.5). Treatment with acitretin may be considered. Clearance occurs spontaneously in 1–3 years. A relapsing childhood type is reported.

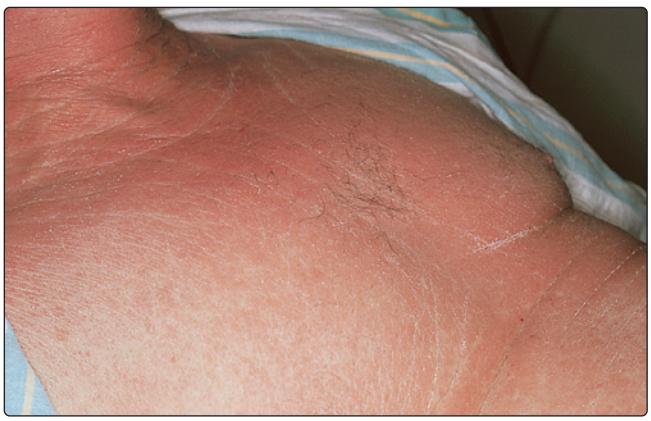


Fig. 23.2 Erythroderma and infiltration of the skin due to Sézary syndrome.

At first, the eruption resembles conventional psoriasis but, when the exfoliative stage is reached, these specific features are lost (Fig. 23.1 and Fig. e23.1). The withdrawal of potent topical steroids or of systemic steroids, or an intercurrent drug eruption, can precipitate erythrodermic psoriasis. Sterile pinhead-sized pustules sometimes develop, and the condition may progress to generalized pustular psoriasis (p. 29).

Epidemiology

PRP is a rare disorder which has been estimated to be identified in 1–10 per 50 000 outpatient visits to dermatology.

The Type I condition classically arises in middle age (30–50 years; approx. 50% cases) or Type III in early life (less than 3–10 years; approx. 10% of cases). Family history is rare. These cases typically resolve within 3–5 years.

Non-classical PRP (as defined by the lack of classical clinical features) can arise in adulthood (Type II) or infancy (Type IV/V) but is associated with a more unpredictable prognosis and often more persistent disease. Some authors have suggested that Type VI PRP describes HIV-associated disease.

Pathogenesis

No clear causality has been identified. However, PRP has been found to arise in association with HIV and other diseases, including autoimmune conditions as well as internal malignancy.

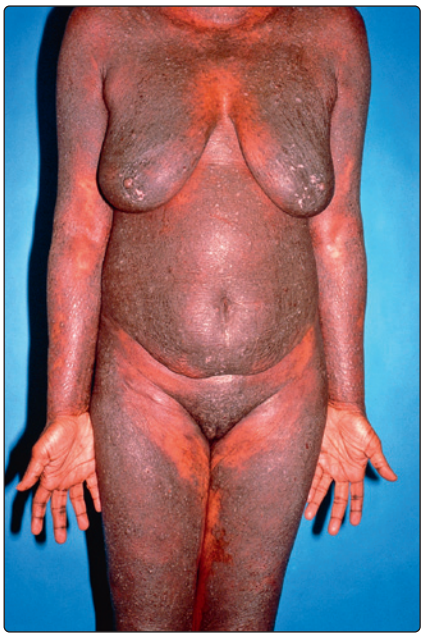


Fig. e23.1 Erythroderma with extensive scaling. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Clinical features

Classical PRP (Types I and III) usually present with cephalo-caudal spread of follicular hyperkeratotic papules forming a red-orange rash. Characteristic hallmarks include patches of normal skin among coalescent involvement, so-called 'islands of sparing', often on the chest or back. At the margins of the coalescent eruption, the follicular nature of the condition may be best visualized. Early in the condition, there is palmar/plantar erythema, which later becomes hyperkeratotic and then frank keratoderma with a waxy surface. With severe persistent facial involvement, ectropion is a common complication.

Type IV PRP is the most common atypical variant and represents approximately 30% of cases. These show localized disease and arise in childhood, usually limited to the extensor surfaces and distal extremities.

Type II PRP differs from Type I by the more eczematous appearance with ichthyosis, alopecia and the slightly scalier keratoderma.

Type V PRP differs from Type III by the younger age of onset and more prominent follicular hyperkeratosis, which may be more likely to be familial.

Treatment

Systemic retinoids are the treatment of choice with most experience using acitretin, and then isotretinoin. Recent data has suggested a role for alitretinoin. Methotrexate is often tried with resistant cases and combination therapy with retinoids may be effective. Phototherapy is of uncertain benefit and has been reported to both exacerbate the condition and to treat it. Other immunosuppressive approaches with azathioprine and ciclosporin may be tried, but as with oral prednisolone, are often ineffective. Treatment options need to be considered in light of the fact that most classical PRP are self-limiting.

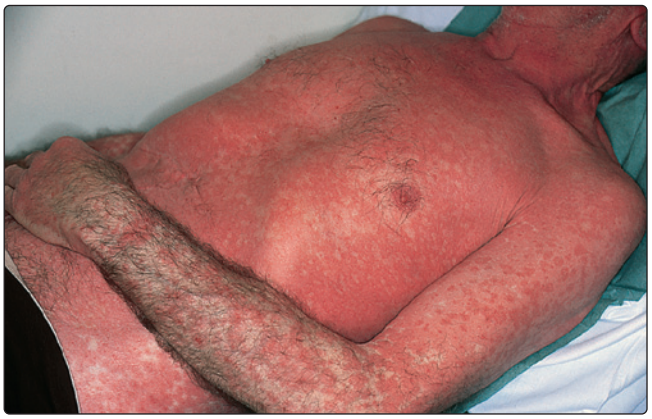


Fig. 23.3 An erythrodermic reaction to an antiinflammatory drug.

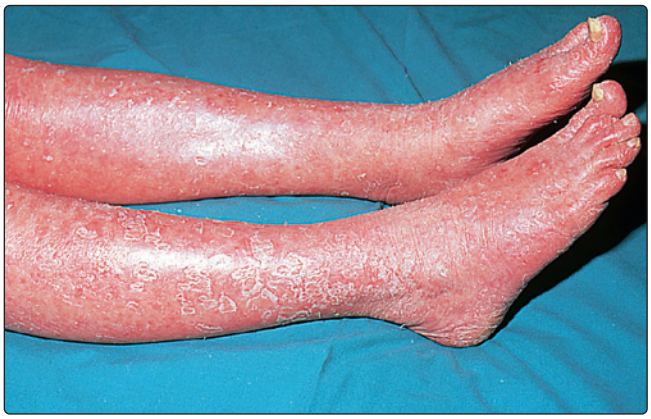


Fig. 23.4 Pityriasis rubra pilaris affecting the legs.

Other dermatoses

Ichthyosiform erythroderma is a type of inherited ichthyosis (p. 94) that is present from birth or early infancy. Acute graft-versus-host disease and, very occasionally, severe scabies or extensive pemphigus can cause erythroderma.

In about 10% of cases of erythroderma, no cause is found. The possibility of a latent lymphoma must be considered.

Complications

Erythroderma is associated with profound physiological and metabolic changes (Table 23.2). Cardiac failure and hypothermia are risks, especially in the elderly, and cutaneous or respiratory infection may also occur. Oedema is almost invariable and cannot be regarded as a sign of heart failure. The pulse rate is always increased. Cardiac failure and infection are difficult to diagnose. Blood cultures are easily contaminated with skin microflora. Lymphadenopathy is common and does not necessarily signify lymphoma. In the pre-steroid era, erythroderma was fatal in one-third of cases, largely due to cardiac failure or infection.

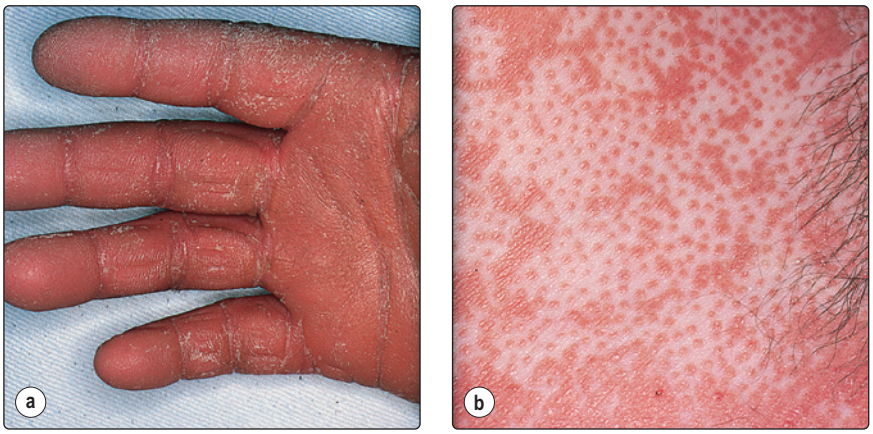


Fig. 23.5 Pityriasis rubra pilaris. (a) Yellowish hyperkeratosis of the palms. (b) Typical follicular lesions.

Table 23.2 **Pathophysiology of erythroderma**

Clinical complication	Pathophysiology
Cardiac failure	Increased skin blood flow Increased plasma volume
Cutaneous oedema	Increased capillary permeability Increased plasma volume Hypoalbuminaemia
Hypoalbuminaemia	Increased plasma volume Reduced albumin synthesis, increased metabolism Protein loss in scaling
Dehydration	Increased transepidermal water loss Increased capillary permeability
Impaired temperature regulation	Excess heat loss Failure to sweat
Dermatopathic lymphadenopathy	Cutaneous inflammation and infection

Management

When the onset is slow, and the patient is not medically compromised, admission may be avoided. For acute cases, inpatient treatment and skilled nursing care are mandatory. The patient is nursed in a comfortably warm room at a steady temperature (preferably 30–32°C), and the pulse, blood pressure, temperature and fluid balance are regularly monitored. A pressure-relieving mattress is sometimes used. Soothing emollient creams and mild-to-moderate topical steroids are a mainstay of local treatment and are often adequate. Systemic steroids are life-saving in severe cases. The maintenance of normal haemodynamics, attention to electrolyte equilibrium and adequate nutritional support (particularly with regard to minimizing protein losses) are vital for severely ill patients. Cardiac failure and intercurrent infections are treated as necessary.

Erythroderma

- A rare but potentially fatal eruption, often of sudden onset, showing near-universal skin involvement.
- Commonest causes: eczema, psoriasis, lymphoma and drug eruption.
- Characterized by hot, red, oedematous, dry and exfoliating skin.
- Complications include cardiac failure, hypothermia, infection and lymphadenopathy.
- Inpatient management and close supervision are required.
- Treatment consists initially of bland emollients and topical steroids. Systemic steroids and full supportive therapy may be needed in life-threatening cases.

24 Photodermatology

Photodermatoses – idiopathic

Polymorphic light eruption

Polymorphic light eruption is often incorrectly referred to as 'prickly heat' (a different condition) and is characterized by pruritic papules, plaques and sometimes vesicles that last for days in light-exposed areas.

Clinical presentation

This is the commonest photodermatosis, and women are affected twice as frequently as men. Pruritic urticated papules, plaques and vesicles develop on light-exposed skin, usually about 24 h after sun or artificial ultraviolet (UV) exposure (Fig. 24.1). It starts in the spring and may persist throughout the summer. The degree of severity is variable.

Differential diagnosis and management

Photoallergic contact dermatitis, drug-induced photosensitivity and lupus erythematosus may need to be considered in the diagnosis of polymorphic light eruption.

The first-line therapy is to use sunscreens and protective measures. A short course of UV therapy (UVB or PUVA) in the late spring can 'harden' the skin so that the patient is able to have a disease-free summer. Oral steroids are useful for acute flares but hydroxychloroquine can be used as a preventative measure.

Chronic actinic dermatitis (actinic reticuloid)

Chronic actinic dermatitis is a rare UV-induced disease of unknown cause affecting middle-aged or elderly men who develop thick plaques of dermatitis on sun-exposed skin.

Histologically, the skin shows a dense lymphocytic infiltrate. Some of the lymphocytes may be atypical and suggest lymphoma (hence the name).

Clinical presentation

There is often a long history of a chronic dermatitis that evolves into a photodermatitis, or a photoallergic contact dermatitis may have been present from the outset. Lichenified plaques of chronic dermatitis form on light-exposed sites and beyond, and are worse in the summer, although the eruption tends to become perennial (Fig. 24.2). The patients are sensitive to the UVA and UVB wavelengths and often to visible light. They may also have a contact or photocontact sensitivity to plant sesquiterpene lactones (air-borne allergens) or to cosmetic ingredients, although the contribution of this to the overall picture is unclear.

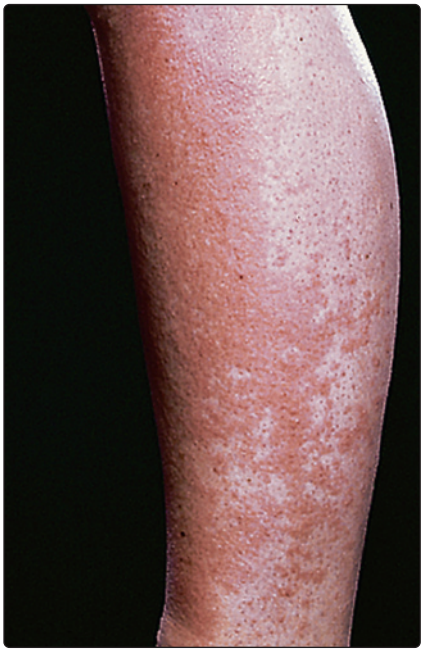


Fig. 24.1 Polymorphic light eruption affecting the lower legs.

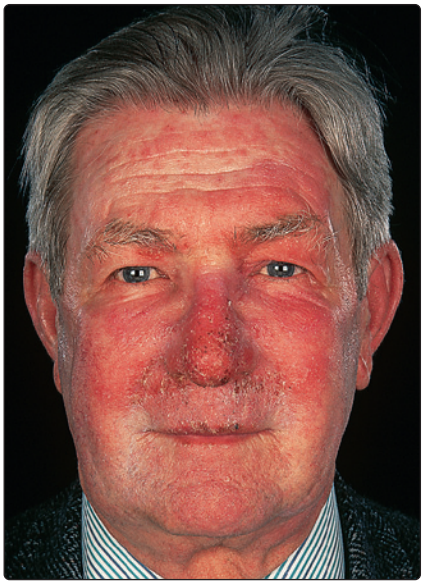


Fig. 24.2 Chronic actinic dermatitis involving the light-exposed areas of the face.

Differential diagnosis and management

Air-borne contact dermatitis or drug-induced photosensitivity may need to be considered, but there is normally little doubt about the diagnosis. Phototesting is helpful.

Light avoidance, sunscreens and topical steroids are used at first in the management of chronic actinic dermatitis. Subsequently, azathioprine, ciclosporin, mycophenolate or systemic steroids may be necessary.

Solar urticaria and actinic prurigo

Solar urticaria and actinic prurigo are rare conditions. In solar urticaria, wheals appear within minutes of exposure to sunlight. Differentiation is required from erythropoietic protoporphyria (below), especially in childhood. Actinic prurigo starts in childhood and is characterized by papules and excoriations, mainly on sun-exposed sites. Actinic prurigo is strongly associated with HLA-DRB1*0401 or 07.

Photodermatoses – other causes

Genetic disorders

Certain rare genetic disorders show photosensitivity. They may have chromosome instability (e.g. Bloom syndrome) or defective DNA repair (e.g. xeroderma pigmentosum, p. 97).

Metabolic disorders

Porphyrias

Porphyrins are important in the formation of haemoglobin, myoglobin and cytochromes. The porphyrias are rare, mostly inherited, metabolic disorders in which deficiencies of enzymes in the porphyrin biosynthetic pathway lead to accumulations of intermediate metabolites. The metabolites are detectable in the urine, faeces and blood, are toxic to the nervous system and cause photosensitivity in the skin.

The main cutaneous porphyrias are the following:

- *Erythropoietic protoporphyria*. Autosomal dominant and starting in childhood, this is a painful red blistering eruption. Pitted linear scars are left on the nose and hands. New therapies designed to induce photoprotection through tanning via synthetic analogues of α-melanocyte-stimulating hormone (MSH) are under trial.
- *Porphyria cutanea tarda*. This is the commonest porphyria, often associated

This is the commonest photodermatosis (Fig. e24.1), and women are affected twice as frequently as men. Pruritic urticated papules, plaques and vesicles develop on light-exposed skin, usually about 24 h after sun or artificial ultraviolet (UV) exposure (Fig. 24.1 and Fig. e24.2). It starts in the spring and may persist throughout the summer. The degree of severity is variable.

There is often a long history of a chronic dermatitis that evolves into a photodermatitis, or a photoallergic contact dermatitis may have been present from the outset. Lichenified plaques of chronic dermatitis form on light-exposed sites and beyond, and are worse in the summer, although the eruption tends to become perennial (Fig. 24.2 and Fig. e24.3). The patients are sensitive to the UVA and UVB wavelengths and often to visible light. They may also have a contact or photocontact sensitivity to plant sesquiterpene lactones (air-borne allergens) or to cosmetic ingredients, although the contribution of this to the overall picture is unclear.

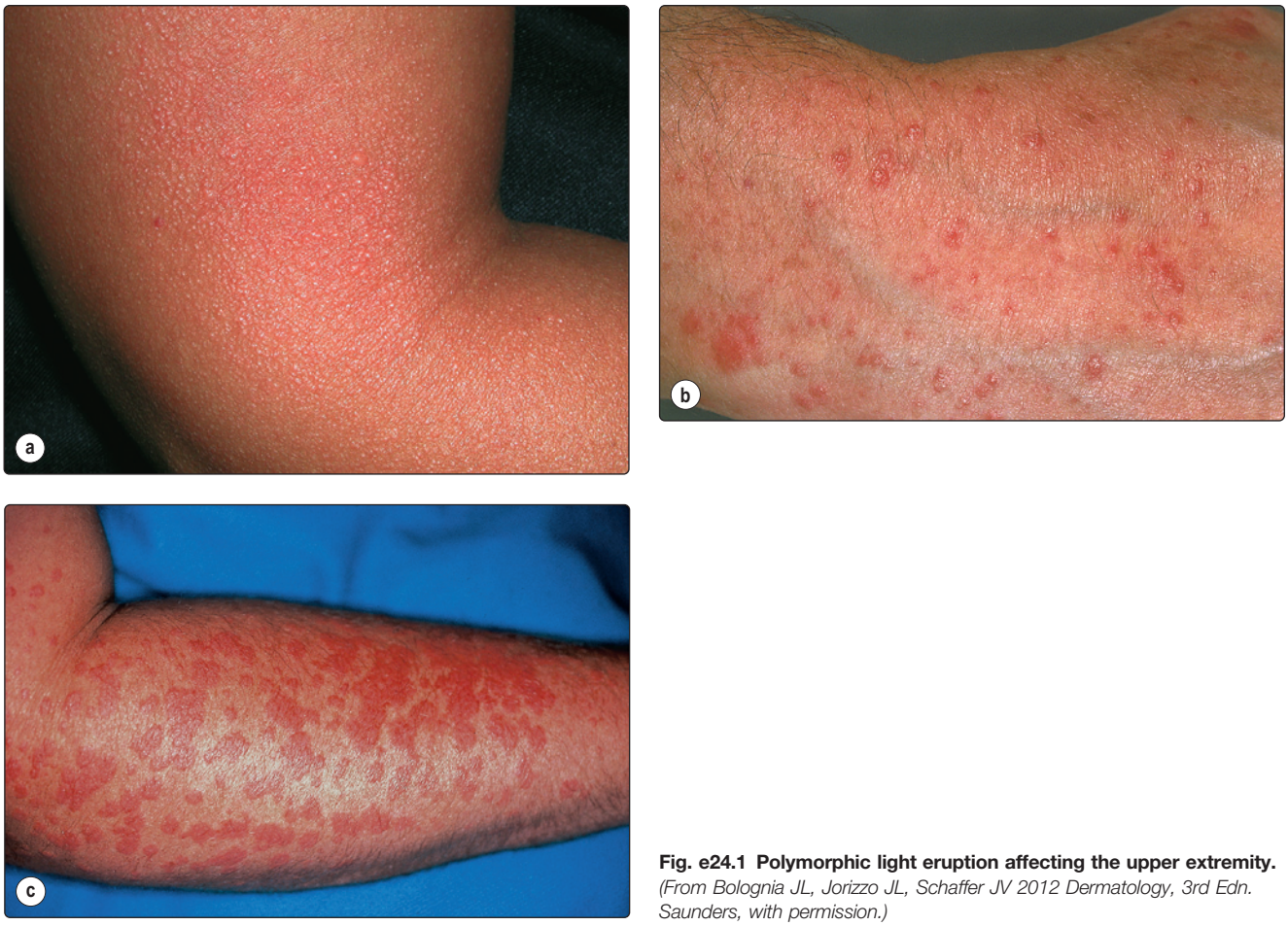


Fig. e24.1 Polymorphic light eruption affecting the upper extremity. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

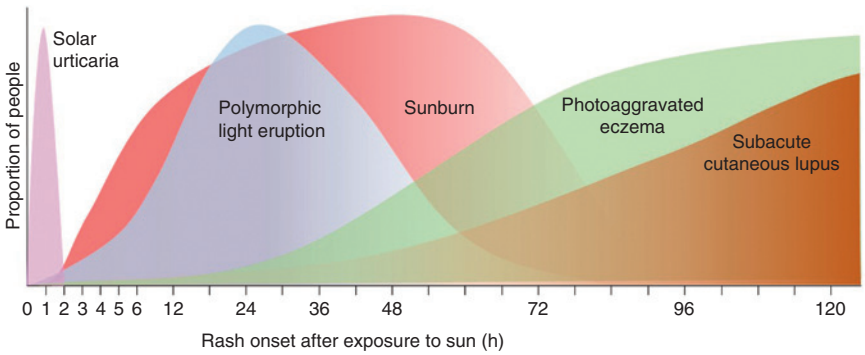


Fig. e24.2 Sun-induced dermatoses.

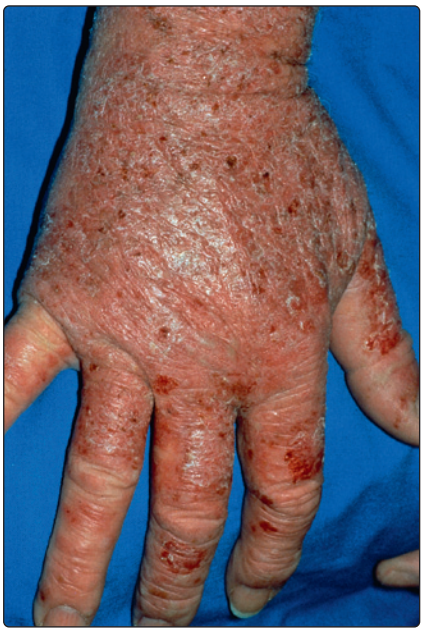


Fig. e24.3 Chronic actinic dermatitis involving the hand. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

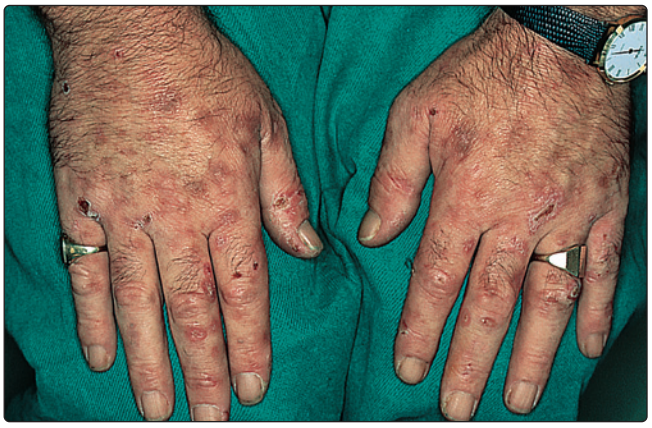


Fig. 24.3 Porphyria cutanea tarda. Changes can be seen on the dorsal aspects of the hands.

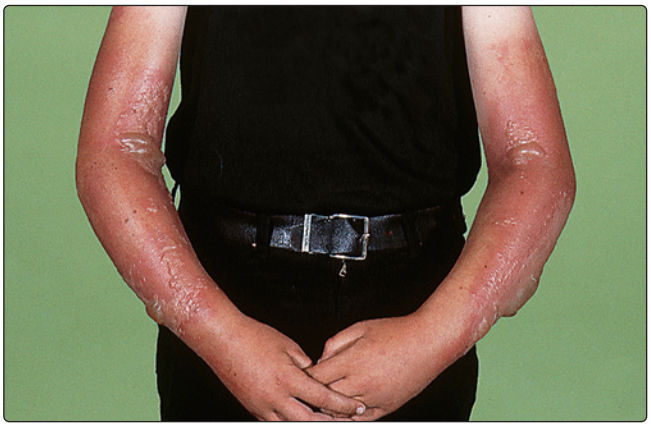


Fig. 24.4 Phytophotodermatitis to common rue. The patient had been gathering the plant in the bright sunlight and developed an extreme bullous reaction. The mechanism is toxic, i.e. irritant, rather than allergic.

with liver disease and frequently alcohol-related. Sun-induced subepidermal blisters on the face and hands (Fig. 24.3) leave fragile, scarred and hairy skin. Alcohol and aggravating drugs (e.g. oestrogens) are avoided. Venesection or low-dose chloroquine therapy may be used.

- *Variegate porphyria*. Autosomal dominant and common in South Africa, the skin signs are like porphyria cutanea tarda. However, acute attacks with abdominal pain and neuropsychiatric symptoms resemble *acute intermittent porphyria*, which has no skin features.

Pellagra

Dietary deficiency of vitamin B3 (nicotinic acid), usually in malnutrition or alcohol abuse, may give a photosensitive dermatitis in association with diarrhoea and dementia.

Due to drugs or chemicals

Drug induced

Several drugs may produce an eruption in light-exposed areas by either toxic (dose-dependent) or allergic mechanisms. The morphology may be eczematous, blistering (e.g. griseofulvin, p. 16), pigmented (e.g. amiodarone, p. 91) or an exaggerated sunburn reaction. Rarely, photo-onycholysis can occur (e.g. with tetracycline). Common photosensitizing drugs are shown in Box 24.1.

Topically applied chemicals

The commonest topical photosensitizers (i.e. allergens) are sunscreen agents (e.g. benzophenones), non-steroidal antiinflammatory drugs (NSAIDs), coal tar derivatives and fragrances. Topical phototoxicity (with an irritant mechanism) is usually due to plant-derived psoralens, as found, e.g. in carrot, celery, fennel, parsnip, common rue and giant hogweed.

Box 24.1 **Drugs causing photosensitivity**

- Amiodarone
- Angiotensin-converting enzyme inhibitors
- Ciprofloxacin
- Furosemide
- Isotretinoin
- Non-steroidal antiinflammatory drugs
- Nifedipine
- Phenothiazines
- Tetracyclines
- Thiazides

Phytophotodermatitis describes a photocontact dermatitis that results from the local photosensitization of the skin through contact with psoralens from a plant (Fig. 24.4). In Berloque dermatitis, streaky pigmentation, often on the sides of the neck, results from the application of perfumes containing psoralens, usually oil of Bergamot (p. 36).

Dermatoses improved or worsened by sunlight

UV improves certain conditions (Table 24.1) and is used as a treatment as natural sunlight, UVB or PUVA. However, benefit is not observed in every case, and UV can, for example, make a patient's psoriasis or atopic eczema worse. The sun may even precipitate psoriasis. The sun can aggravate several other conditions (listed in Table 24.1).

Table 24.1 **Dermatoses improved or aggravated by sunlight**

Improved	Worsened or provoked
Acne	Atopic eczema (approx. 30%)
Atopic eczema	Herpes simplex
Mycosis fungoides	Lupus erythematosus
Pityriasis rosea	Porphyrias
Psoriasis	Rosacea
Uraemic pruritus	Vitiligo

Photodermatology

- In normal skin, sunlight can cause tanning, sunburn, photoageing (p. 112) and photocarcinogenesis (Ch. 53).
- The important idiopathic photodermatoses are polymorphic light eruption, chronic actinic dermatitis and solar urticaria.
- Dermatoses worsened by sunlight include some eczema, herpes simplex, lupus erythematosus, cutaneous porphyrias, rosacea and vitiligo.
- Dermatoses improved by sunlight include acne, atopic eczema, mycosis fungoides, pityriasis rosea, psoriasis and the pruritus of renal failure.
- Drugs that are not infrequent causes of photosensitivity include tetracyclines, phenothiazines, angiotensin-converting enzyme (ACE) inhibitors, non-steroidal antiinflammatory drugs (NSAIDs), furosemide and thiazides.

25 Bacterial infection – Staphylococcal and streptococcal

The skin is a barrier to infection but, if its defences are penetrated or broken down, numerous micro-organisms can cause disease (Table 25.1).

Table 25.1 **Bacterial diseases of the skin**

Organism	Infection
Commensals	Erythrasma, pitted keratolysis, trichomycosis axillaris
Staphylococci	Impetigo, ecthyma, folliculitis, secondary infection
Streptococci	Erysipelas, cellulitis, impetigo, ecthyma, necrotizing fasciitis
Gram-negative	Secondary infection, folliculitis, cellulitis
Mycobacterial	TB (lupus vulgaris, warty tuberculosis, scrofuloderma), fish tank granuloma, Buruli ulcer, leprosy
Spirochaetes	Syphilis (e.g. primary, secondary), Lyme disease (erythema chronicum migrans)
Neisseria	Gonorrhoea (pustules), meningococcaemia (purpura)
Others	Anthrax (pustule), erysipeloid (pustule)

The normal skin microflora

Normal skin has a resident flora of usually harmless micro-organisms, including bacteria, yeasts and mites (see also Ch. 5). Recent work, utilizing novel culture independent analysis, has identified that the most predominant genera are corynebacteria (22.8%; diphtheroids), propionibacteria (23.0%) and staphylococci (16.8%). Interestingly, there is more similarity in microbial diversity in the same anatomical location between individuals than between different anatomical locations in the same individual. Micrococci, e.g. number 0.5 million/cm^2 in the axilla but only 60/cm^2 on the forearm. Some individuals are high carriers.

Staphylococcal infections

A third of people intermittently carry *Staphylococcus aureus* in the nose or, less often, the axilla or perineum. Staphylococci can infect the skin directly or secondarily, as in eczema or psoriasis.

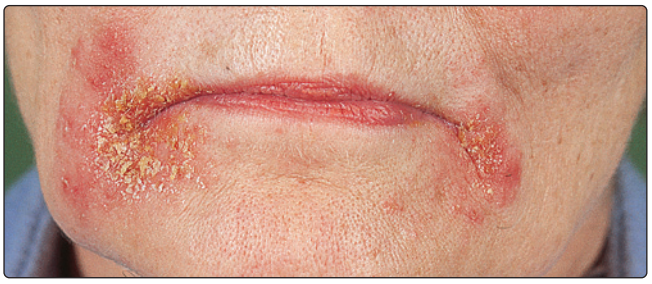


Fig. 25.1 Impetigo of the face due to *Staphylococcus aureus*.

Impetigo

Impetigo is a contagious superficial skin infection caused by either staphylococci or streptococci, or both.

Clinical presentation

Impetigo is now relatively uncommon in the UK, mainly because of improved social conditions, but it is endemic in developing countries. It generally occurs in children and presents as thin-walled, easily ruptured vesicles, often on the face, which leave areas of yellow-crusted exudate (Fig. 25.1). Lesions spread rapidly and are contagious. A bullous form (Fig. 25.2), with blisters 1–2 cm in diameter, is seen in all ages and affects the face or extremities. Atopic eczema, scabies, herpes simplex and lice infestation may all become impetiginized. Impetigo can be confused with herpes simplex or a fungal infection.

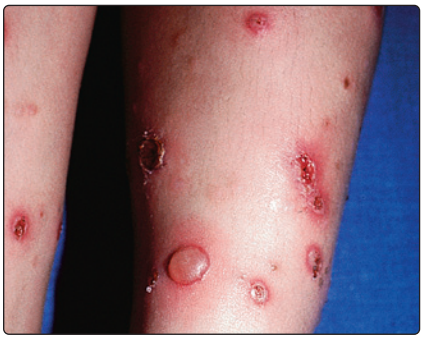


Fig. 25.2 Bullous impetigo results from Staphylococcal toxin production. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permisssion.)*

Management

Most localized cases respond to the removal of the crusts with saline soaks and the application of a topical antibiotic (e.g. mupirocin, fusidic acid or neomycin/bacitracin). Systemic flucloxacillin or erythromycin is given for widespread infection. Impetigo caused by *Streptococcus pyogenes* may result in glomerulonephritis, a serious complication. Methicillin-resistant *Staph. aureus* (MRSA) carriage (and infection) has increased with the widespread use of antibiotics.

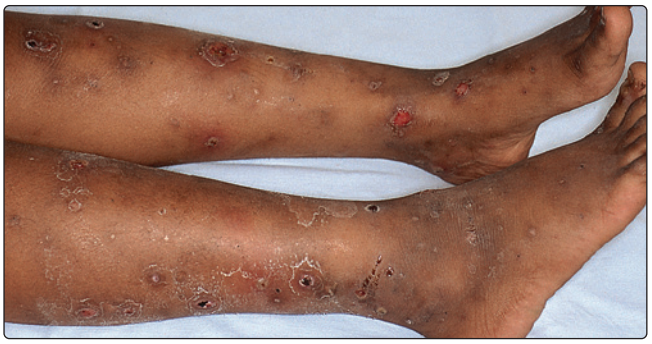


Fig. 25.3 Ecthyma, due to a streptococcus, affecting the lower legs.

Ecthyma

Ecthyma is characterized by circumscribed, ulcerated and crusted infected lesions that heal with scarring. An insect bite or neglected minor injury may become infected with staphylococci or streptococci (or both). Ecthyma mostly occurs on the legs (Fig. 25.3) and may be seen in drug addicts or debilitated patients. Treatment is with systemic and topical antibiotics.

Folliculitis and related conditions

Infection can affect hair follicles. *Folliculitis* is an acute pustular infection of multiple hair follicles; a *furuncle* is an acute abscess formation in adjacent hair follicles; and a *carbuncle* is a deep abscess formed in a group of follicles giving a painful suppurating mass.

Clinical presentation

Follicular pustules are seen in hair-bearing areas, e.g. the legs, scalp or face. In men, folliculitis may affect the beard area (sycosis barbae). In women, it may occur on the legs after hair removal by shaving or waxing. *Staphylococcus aureus* is usually, but not invariably, responsible. Strains carrying the virulence

A third of people intermittently carry *Staphylococcus aureus* in the nose or, less often, the axilla or perineum. Staphylococci can infect the skin directly or secondarily, as in eczema or psoriasis (eFig. 25.1).

Staphylococcus aureus life cycle (see Fig. e25.1)

Early on during colonization *Staphylococcus aureus* (SA) downregulates virulence factors and utilizes its intrinsic structures (cell wall and polysaccharide capsule) to prevent host responses. In addition, SA secretes protein-A, which binds host antibodies, preventing their function. One of the earliest classes of proteins expressed include microbial surface components recognizing adhesive matrix molecules (MSCRAMMs), including platelet clumping factor B and iron-regulated surface determinant A. When the SA colonization is secured, the population senses the quorum of SA bacteria through a paracrine signalling system regulated through the AGR gene. AGR signalling induces expression of toxins such as Panton–Valentine leucocidin, which damage host cells and allows invasion of the SA into the tissues.

Staphylococcus aureus toxins

Staphylococcus aureus can secrete a variety of toxins as indicated in Table e25.1.

Impetigo is now relatively uncommon in the UK, mainly because of improved social conditions, but it is endemic in developing countries. It generally occurs in children and presents as thin-walled, easily ruptured vesicles, often on the face, which leave areas of yellow-crusted exudate (Fig. 25.1 and eFig 25.2). Lesions spread rapidly and are contagious. A bullous form, with blisters 1–2 cm in diameter, is seen in all ages and affects the face or extremities. Atopic eczema, scabies, herpes simplex and lice infestation may all become impetiginized. Impetigo can be confused with herpes simplex or a fungal infection.

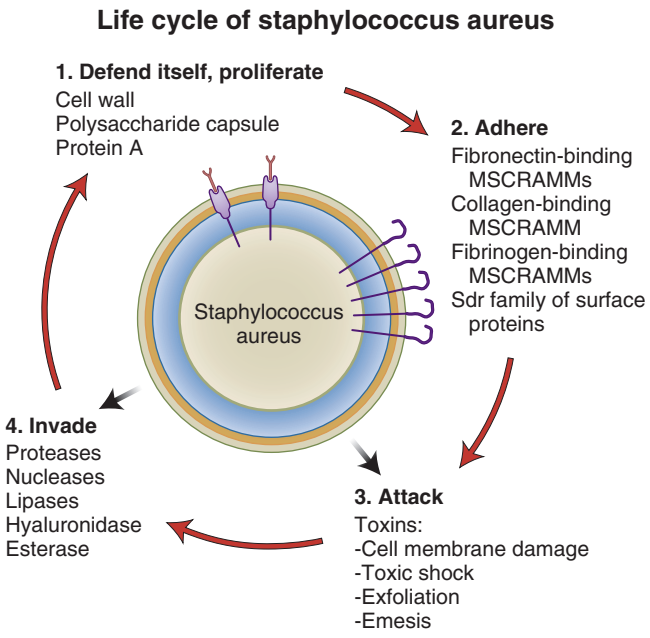


Fig. e25.1 Life cycle of *Staphylococcus aureus*.

Table e25.1 **Toxins secreted by *Staphylococcus aureus***

Virulence factor	Disease
Superantigen	
Enterotoxin A Enterotoxin B Enterotoxin C Enterotoxin D Enterotoxin E	Food poisoning, toxic shock syndrome (TSS)
Toxic shock syndrome toxin-1	TSS, neonatal TSS-like exanthematous disease (NTED)
Exfoliative toxin A Exfoliative toxin B	Bullous impetigo (eFig. 25.3), Staphylococcal scalded skin syndrome (eFig. 25.4)
Exfoliative toxin D	Deep-seated infections
Cytotoxin	
α-Haemolysin β-Haemolysin γ-Haemolysin	Haemolysis, necrosis
δ-Haemolysin	?
Panton–Valentine leukocidin	Leukolysis, necrosis, deep-seated infections

(Adapted from Iwatsuki K, Yamasaki O, Morizane S, Oono T. 2006. Staphylococcal cutaneous infections: invasion, evasion and aggression. J Dermatol Sci 42(3):203–214.)

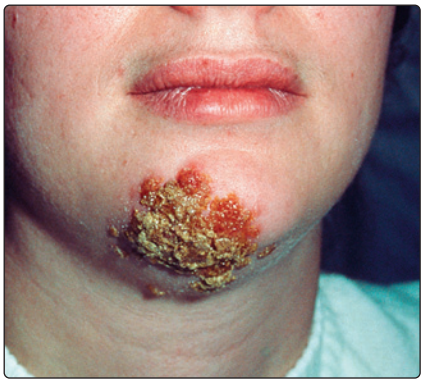


Fig. e25.2 Impetigo of the face. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

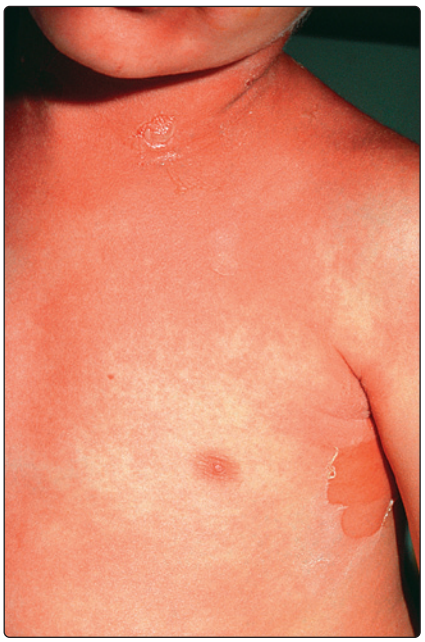


Fig. e25.3 Staphylococcal scalded skin syndrome. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

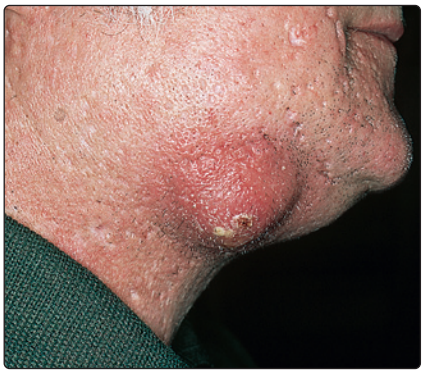


Fig. 25.4 A carbuncle. This required surgical drainage. The patient had had previous staphylococcal infection.

factor Panton–Valentine leukocidin (PVL) are associated with more aggressive disease (eFig. 25.3). A Gram-negative folliculitis (e.g. with *Pseudomonas*) may occur with prolonged antibiotic treatment for acne. *Pityrosporum folliculitis* is a separate condition due to a commensal yeast (p. 62).

Furuncles (boils) present as tender red pustules that suppurate and heal with scarring. They often occur on the face, neck, scalp, axillae and perineum. Some patients have recurrent staphylococcal boils of the axillae or perineum. Large suppurating carbuncles (Fig. 25.4) due to *Staph. aureus* may cause systemic upset. Distinction from hidradenitis suppurativa is important (p. 69).

Management

Swabs for bacterial culture are taken from the lesion and from carrier sites, e.g. the nose, axilla and groin. Obesity, diabetes mellitus and occlusion from clothing are predisposing factors. Acute staphylococcal infections are treated with antibiotics, both systemic (e.g. flucloxacillin or erythromycin) and topical (e.g. fusidic acid, mupirocin or neomycin/bacitracin). Chronic and recurrent cases are more difficult. Carrier sites, e.g. the nose, need treatment with a topical antibiotic (e.g. mupirocin). General measures such as improved hygiene, regular bathing or showering and the use of antiseptics in the bath and on the skin (e.g. chlorhexidine) can help, but courses of oral antibiotics may be needed. Carbuncles often need prompt surgical drainage. An infrequent complication is thrombosis in the cavernous sinus, associated with facial infection.

Staphylococcal scalded skin syndrome

Staphylococcal scalded skin syndrome is an acute toxic illness, usually of infants, in which there is shedding of sheets of epidermis associated with localized staphylococcal infection in the skin or elsewhere. Large sheets of superficial epidermis are shed, resembling a scald, leaving denuded erythematous areas. Staphylococci release epidermolytic toxins into the bloodstream which damage desmoglein 1 in the outer epidermis and causes the epidermis to split. The same level of epidermal split is seen in pemphigus foliaceus due to autoimmune IgG targeting the same protein (p. 94).

Although a serious condition requiring inpatient treatment, the prognosis is good when systemic flucloxacillin or erythromycin is prescribed.

Streptococcal infections

Strep. pyogenes, the principal human skin pathogen, is occasionally found in the throat and may persist after an infection. It is sometimes carried in the nose and can contaminate and colonize damaged skin.

Erysipelas

Erysipelas is an acute infection of the dermis by *Strep. pyogenes*. It shows well-demarcated raised erythema, oedema and skin tenderness.

Clinical presentation

The skin lesions may be preceded by fever, malaise and 'flu-like' symptoms. Erysipelas usually affects the face (where it may be bilateral) or the lower leg, and appears as a painful hot red swelling (Fig. 25.5). The lesion has a well-defined edge and may blister. Cellulitis may coexist. The streptococci usually gain entry to the skin via a fissure, e.g. behind the ear, or associated with tinea pedis between the toes.

Differential diagnosis and complications

On the face, erysipelas may be confused with angioedema or allergic contact dermatitis, but the condition is usually distinguishable as it causes tenderness and systemic upset. Recurrent attacks in the same place can result in lymphoedema due to lymphatic damage.

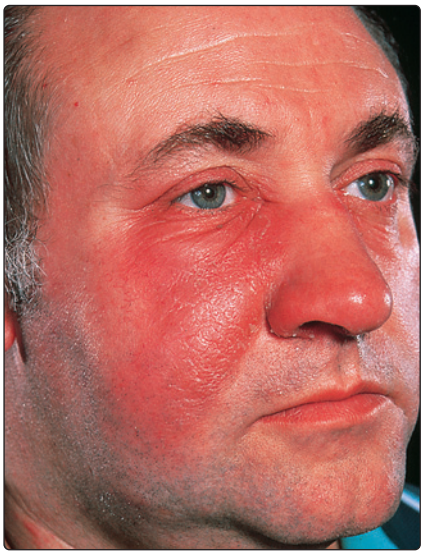


Fig. 25.5 Erysipelas of the right cheek due to a streptococcal infection.

A fatal streptococcal septicaemia can occur in debilitated patients. Guttate psoriasis (p. 28) and acute glomerulonephritis may follow a streptococcal infection.

Management

A good response is usually seen with prompt treatment. Topical therapy is inappropriate, and penicillin should be prescribed. *Strep. pyogenes* is nearly always sensitive. Intravenous treatment is needed at first for a severe infection, usually with benzylpenicillin for about 2 days. Oral penicillin V can then be given for 7–14 days. In less severe cases, penicillin V is adequate. Erythromycin is used if there is penicillin allergy. Recurrent erysipelas, i.e. more than two episodes at one site, requires prophylactic long-term penicillin V (250–500 mg once or twice a day), with attention to hygiene at potential portals of entry.

Necrotizing fasciitis

Necrotizing fasciitis is an acute and serious infection. It usually occurs in otherwise healthy subjects after minor trauma. An ill-defined erythema, often on the head or limbs and associated with a high fever, rapidly becomes necrotic. Early surgical debridement and systemic antibiotics are essential.

Staphylococcal and streptococcal infections

- **Normal skin microflora** includes corynebacteria, propionibacteria and staphylococci, and may number 0.5 million/cm^2. Some individuals are higher carriers than others.
- **Staphylococcal infection** of the skin may be primary, e.g. impetigo, ecthyma or folliculitis, or secondary, e.g. superinfection of eczema, psoriasis or leg ulcers.
- **Streptococcal infections** may also be primary, e.g. erysipelas or cellulitis, or secondary, e.g. infection of dermatoses or leg ulcers.

26 Other bacterial infections

Diseases due to commensal overgrowth

Sometimes, 'normal' commensals can result in disease. Among the most common are the following:

- *Pitted keratolysis*. Overgrowth of resident micro-organisms that digest keratin; occurs with occluding footwear and sweaty feet (Fig. 26.1). Malodorous pitted erosions and punched out, discoloured areas result. Better hygiene, topical neomycin or soaks with 0.01% aqueous potassium permanganate or 3% aqueous formaldehyde usually help.
- *Erythrasma*. A dry, reddish-brown, slightly scaly and usually asymptomatic eruption that affects the body folds (Fig. 26.2). It fluoresces coral pink with Wood's light, owing to the production of porphyrins by the corynebacteria. Imidazole creams, topical fusidic acid or oral erythromycin are effective.
- *Trichomycosis axillaris*. Overgrowths of corynebacteria form yellow concretions on axillary hair. Topical antimicrobials usually effect a cure.

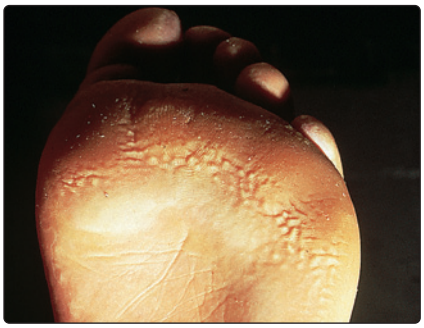


Fig. 26.1 Pitted keratolysis, due to overgrowth of resident micro-organisms.

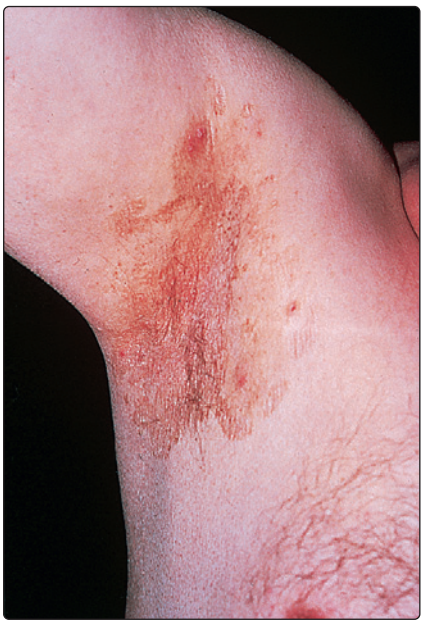


Fig. 26.2 Erythrasma affecting the axilla. This was caused by overgrowth of corynebacteria.

Mycobacterial infections

Mycobacterium tuberculosis and *M. leprae* (p. 64) are the most important mycobacteria in human disease, although other species can cause infections. In Western countries, tuberculosis (TB) has recently shown resurgence, related to immigration and co-infection with HIV. In the developing world, 50% of HIV-infected individuals also have TB. Individuals treated with anti-TNF biologics (e.g. for psoriasis) are at particular risk and latent TB should be excluded before treatment. TB can produce a number of cutaneous manifestations (Box 26.1).

Box 26.1 **Skin manifestations of TB**

Lupus vulgaris: reddish-brown plaques, e.g. on neck.

Scrofuloderma: skin involved from underlying node.

Warty tuberculosis: warty plaques, e.g. on buttock.

Tuberculides: cutaneous hypersensitivity reactions.

Diagnosis

Diagnosis of mycobacterial infections in the skin is confirmed with microbiological culture from a skin biopsy. This requires specific culture conditions so the clinical information should be made clear to the laboratory staff. Culture results are usually very delayed and can take 8–12 weeks.

Following confirmation by culture, PCR analysis for mycobacterial DNA is useful to identify mycobacterial subtypes and can give a clue to the likelihood of resistance to therapy, but requires a high mycobacterial load in the sample to gain positive results and is not generally useful for diagnostic testing. Skin histology can identify acid fast bacilli with Ziehl–Neelsen staining but this is unreliable. T cell interferon-γ release assays (IGRAs) to the *Mycobacterium tuberculosis* antigen are highly specific (for current or latent infection) and reasonably sensitive and have largely replaced other tests. Although IGRAs may show positivity with mycobacteria other than TB, this is variable and not reliable for diagnosis. The most widely used IGRAs are:

- QuantiFERON®-TB Gold in-tube test (QFT-GIT)
- T-SPOT®. TB test (T-Spot).

Lupus vulgaris

Reddish-brown plaques, often on the head or neck, characterize lupus vulgaris. It is the commonest *M. tuberculosis* skin infection.

Clinical presentation

Lupus vulgaris follows primary inoculation and develops in individuals with some immunity. It begins as painless reddish-brown nodules that slowly enlarge to form a plaque (Fig. 26.3), leaving scarring and sometimes destruction of deeper tissues such as cartilage. Presentation in the elderly is often due to reactivation of inadequately treated pre-existing disease.

Differential diagnosis and complications

Papules of lupus vulgaris typically show an 'apple-jelly' colour when compressed with a glass slide (diascopy). A biopsy will reveal tuberculoid granulomata with a few bacilli. The Mantoux test is positive. Sometimes it is necessary to consider:

- morphoeic basal cell carcinoma
- sarcoidosis or leprosy
- discoid lupus erythematosus
- dermatophyte infection (ringworm).

Scrofuloderma

A tuberculous lymph node or joint can directly involve the overlying skin, often on the neck and in children. Fistulae and scarring result.

Warty tuberculosis

A warty reddish or brown plaque, frequently on the hands, knees or buttock,

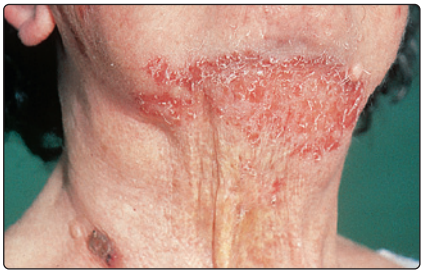


Fig. 26.3 Lupus vulgaris, due to *M. tuberculosis*.

- *Erythrasma*. A dry, reddish-brown, slightly scaly and usually asymptomatic eruption that affects the body folds (Fig. 26.2 and Fig. e26.1). It fluoresces coral pink with Wood's light, owing to the production of porphyrins by the corynebacteria. Imidazole creams, topical fusidic acid or oral erythromycin are effective.

Lupus vulgaris follows primary inoculation and develops in individuals with some immunity. It begins as painless reddish-brown nodules that slowly enlarge to form a plaque (Fig. 26.3 and Fig. e26.2), leaving scarring and sometimes destruction of deeper tissues such as cartilage. Presentation in the elderly is often due to reactivation of inadequately treated pre-existing disease.

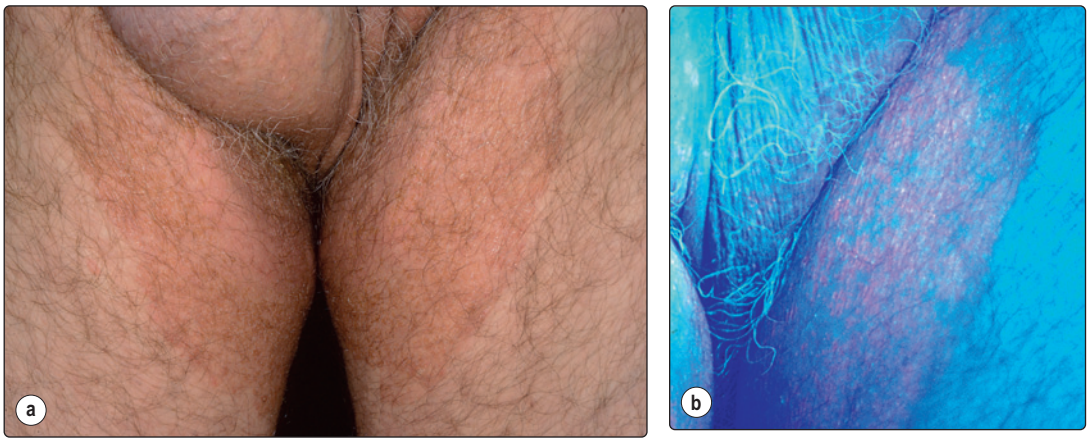


Fig. e26.1 Erythrasma of the groins (a). Coral pink fluorescence with Wood's light is typical (b). *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

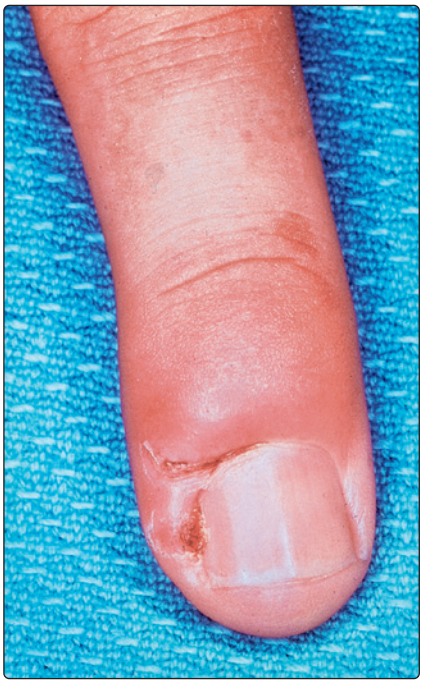


Fig. e26.2 Sporotrichoid (lymphatic) spread of *Mycobacterium marinum*. Commonly acquired by keepers of tropical fish, while cleaning the tank. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

results from inoculation of TB bacilli into the skin of someone with immunity from previous infection. It is rare in Western countries, but is a common form of cutaneous TB in the developing world.

Tuberculides

Squamous cell carcinoma may develop in longstanding scarred lesions. The presence of *M. tuberculosis* somewhere in the body can induce cutaneous reactions called 'tuberculides'. *Erythema nodosum* (p. 87) is the best known example. Another is *erythema induratum*, which occurs as painful ulcerating nodules on the lower legs of women and is thought to be a hypersensitivity response to TB.

Management

Four drugs, normally rifampicin, isoniazid, pyrazinamide and ethambutol, are given for the initial 8 weeks. After this, isoniazid and rifampicin are continued to complete a 6-month course. Directly observed therapy, in which ingestion of drugs is witnessed, improves cure rates if compliance could be a problem. Adverse reactions to TB drugs are common.

Other cutaneous mycobacterial infections

Fish tank granuloma

Classically, this is a reddish, slightly scaly plaque on the hand or arm of someone who keeps tropical fish. It is due to *Mycobacterium marinum*, which infects fish and is also found in swimming pools, sea water and fresh water. The infection usually enters via a portal on the distal limb (e.g. abrasion to finger) and induces a chronic wound which fails to heal. Subsequent lymphatic spread results in nodules arising proximally up the limb. *Mycobacterium marinum* culture is often negative and the diagnosis may need to be made clinically. Oral clarithromycin is usually effective.

Spirochaetal infections

Spirochaetes are thin, spiral and motile organisms. Syphilis (p. 126), due to *Treponema pallidum*, is the best known spirochaetal disease, but other spirochaetes, e.g. *Borrelia burgdorferi*, can be pathogenic.

Non-venereal treponemal infections

Non-venereal treponemal infections are endemic in tropical and subtropical areas where people live in conditions of extreme poverty. They are caused by spirochaetes that are very similar to *T. pallidum*. Serological tests for syphilis are positive. All three of the following diseases respond to long-acting penicillins.

- *Yaws* occurs in Central Africa, Central America and South-east Asia. In children, the treponeme enters the skin through an abrasion and, after a few weeks, results in an ulcerated papilloma that heals with scarring. Secondary lesions follow and, in the late stage, bone deformities develop.
- *Bejel* (endemic syphilis), found in rural Middle Eastern tribes living in unhygienic conditions, is similar to yaws but starts around the mouth. It is transmitted by skin contact.
- *Pinta* is confined to central and south America. It results in hyperkeratoses over extensor aspects of joints with both hypo- and hyperpigmentation.

Lyme disease

Lyme disease is a cutaneous and systemic infection caused by the spirochaete *Borrelia burgdorferi* and spread by tick bite. Most cases have been reported in the USA and Europe. At the site of the tick bite, usually a limb, a slowly expanding erythematous ring (erythema chronicum migrans) develops (Fig. 26.4). Arthritis and neurological and cardiac disease may follow. A response to high-dose amoxicillin or doxycycline is usual.

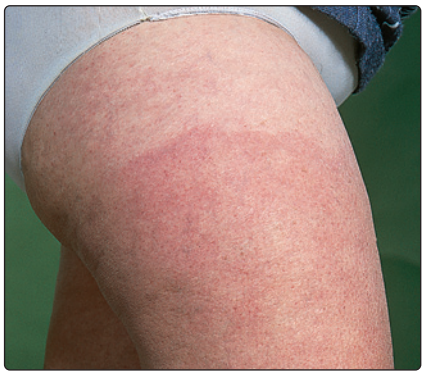


Fig. 26.4 Erythema chronicum migrans of Lyme disease.

Further bacterial infections

Gram-negative infections

Bacilli such as *Pseudomonas aeruginosa* can infect skin wounds, notably leg ulcers. They may also cause folliculitis and cellulitis.

Cellulitis

Cellulitis is an infection of the subcutaneous tissues. It is often due to streptococci, but is deeper and more extensive than erysipelas. The cardinal features are swelling, redness and local pain with systemic upset and fever. The leg is often affected (Fig. 26.5). The organism may gain entry through fissures between the toes or via a leg ulcer. Lymphangitis is common, and lymphatic damage may result. Hospital admission is usually indicated, particularly if the leg is involved. Antistreptococcal antibiotics are given for straightforward cases. However, a broad-spectrum antibiotic is prescribed for cellulitis complicating a leg ulcer, because a selection of organisms may be responsible. Blood cultures and ulcer swabs may give some guidance. Recent clinical trials (PATCH I & II) have shown convincing evidence to support the use of prophylactic penicillin V 250 mg twice daily for 6 months following first episode and 12 months in recurrent cellulitis.

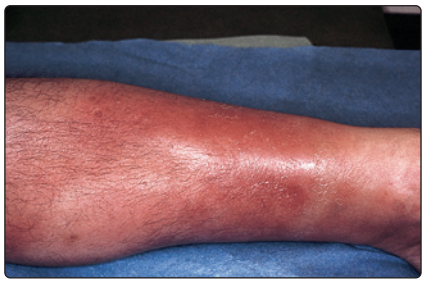


Fig. 26.5 Cellulitis affecting the lower leg.

Other bacterial infections

- Overgrowth of commensal organisms can result in minor skin 'disease'.
- Cutaneous mycobacterial infection is mainly due to *M. tuberculosis*, but occasionally 'atypical' mycobacteria such as *M. marinum* cause disease.
- *M. tuberculosis* latent or active infection can be diagnosed by interferon-γ release assays (IGRA).
- Lyme disease is a tick-transmitted infection with *Borrelia burgdorferi*; the skin signs are often associated with arthritis or neurological disease.
- Cellulitis often affects the leg and is frequently caused by streptococci, although other organisms may be involved.

Buruli ulcer

In tropical zones, *Mycobacterium ulcerans* – acquired from vegetation or water after trauma – produces a painless erythematous nodule usually on the leg or forearm. The nodule becomes necrotic and ulceration results.

Disseminated infection with *Mycobacterium avium* complex is seen in patients with HIV infection (p. 58).

Blacklegged ticks (*Ixodes ricinus* in the UK, *Ixodes scapularis* in the USA) feed on the blood of animals and people. They may become infected with *Borrelia burgdorferi* and, if they land on humans, may transmit the disease. The natural habitat for ticks are small mammals, deer and sheep. Ticks are very small. The first sign of infection is erythema chronicum migrans (Fig. 26.4), an erythematous patch enlarging slowly around the site of the tick bite. Once discovered, ticks should be removed as soon as possible. To do so the mouth parts should be grabbed by fine forceps/tweezers or a tick removal tool and the tick pulled away from the skin. Remove the tick as soon as possible. Engorged ticks have a higher chance of having spread *Borrelia* to the human and, therefore, empirical treatment or later testing is recommended. Removed ticks can be tested for the infection themselves, which if negative will mean that the individual does not need treatment. Following the tick removal, clean the bite with antiseptic because bacterial infection is also common. In a non-engorged tick bite, no blood test or empirical antibiotics are generally recommended. Erythema chronicum migrans after tick bite should prompt treatment with Doxycycline 100 mg twice daily for 10–14 days or amoxicillin/clavulanic acid.

Anthrax

A haemorrhagic bulla, associated with oedema and fever, forms at the site of inoculation of the skin with *Bacillus anthracis*, usually from contaminated animal products. It is now rare. Ciprofloxacin or amoxicillin is curative.

27 | **Viral infections** – Warts and other viral infections

Unlike bacteria and yeasts, viruses are not thought to exist on the skin surface as commensals. However, studies in patients with viral warts have shown viral DNA in epidermal cells of seemingly normal skin next to warty areas.

Viral warts

Warts (verrucae) are common and benign cutaneous tumours due to infection of epidermal cells with human papillomavirus (HPV).

Aetiopathogenesis and pathology

Over 100 subtypes of DNA HPV have been identified. The virus infects by direct inoculation and is caught by touch, sexual contact or at the swimming baths. Certain HPV subtypes are associated with specific clinical lesions, e.g. types 2, 27 and 57 with common hand warts; types 1, 2, 4, 27 and 57 with plantar warts; types 3 and 10 with plane warts; types 6 and 11 with anogenital warts. Anogenital HPV subtypes (e.g. 16 and 18) cause cytological dysplasia of the cervix, penis and perianal region, which may be precancerous. Immunosuppressed individuals, such as those with organ transplants, are particularly susceptible to viral warts (p. 59). Infection with the wart virus infection causes the epidermis to be thickened and hyperkeratotic. Keratinocytes in the granular layer show vacuolation.

Clinical presentation

Certain clinical patterns are well recognized:

- *Common warts*. These present as dome-shaped papules or nodules with a papilliferous surface. They are usually multiple, and are commonest on the hands (Fig. 27.1) or feet in children but also affect the face and genitalia. Their surface interrupts skin lines. Some facial warts are 'filiform' with fine digit-like projections.
- *Plane warts*. These are smooth flat-topped papules, often slightly brown in colour, and commonest on the face (Fig. 27.2) and dorsal aspects of the hands. They are usually multiple and resist treatment, but eventually resolve spontaneously, often after becoming inflamed. They can show the Koebner phenomenon.
- *Plantar warts*. These are seen in children and adolescents on the soles of the feet; pressure causes them to grow into the dermis. They are painful and covered by callus, which, when pared, reveals dark punctate spots (thrombosed capillaries). Mosaic warts are plaques on the soles that comprise multiple individual warts.
- *Anogenital warts*. In males, these affect the penis and, in men who have sex with men, the perianal area. In females, the vulva, vagina and perianal area may be involved (Fig. 27.3). The warts may be small or may coalesce into large cauliflower-like 'condylomata acuminata'. Proctoscopy (if perianal warts are present) and colposcopy (for female genital warts) are needed to identify and treat any anal or cervical intraepithelial neoplasia or invasive carcinoma (p. 128). Sexual partners need to be examined.

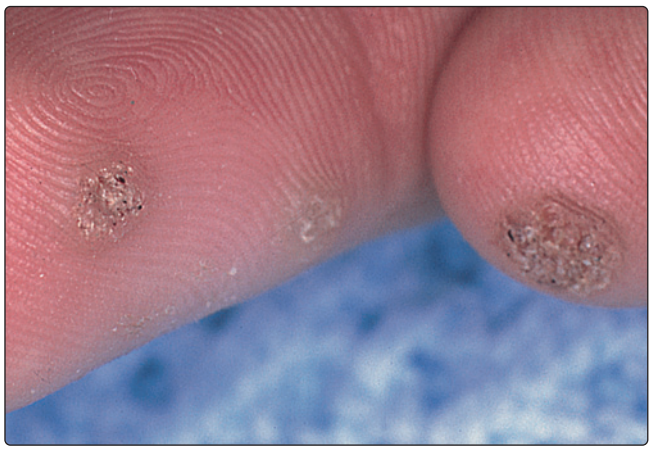


Fig. 27.1 Common viral warts on the hand.

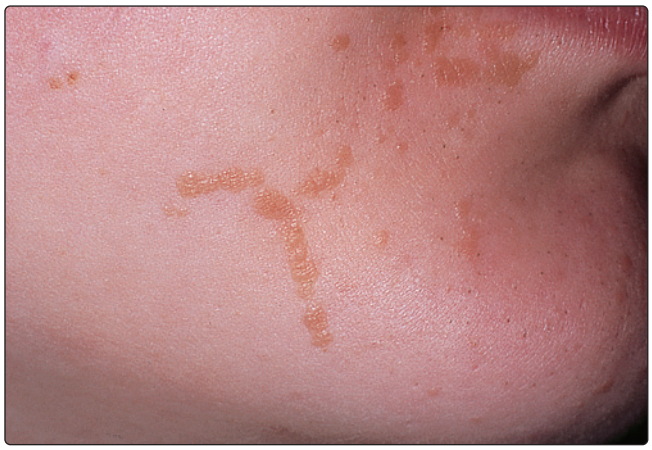


Fig. 27.2 Plane viral warts on the face, showing a linear distribution.

Differential diagnosis and complications

The diagnosis of viral warts is usually obvious. Occasionally, corns on the sole or hand, or molluscum contagiosum elsewhere, are confused. With viral warts under the fingernails and toenails, it is important to consider amelanotic malignant melanoma, periungual fibroma (of tuberous sclerosis, p. 96) and bony subungual exostosis. Anogenital warts may resemble the condyloma lata of secondary syphilis. Vulval, penile and anal intraepithelial neoplasia (sometimes called 'Bowenoid papulosis') can resemble viral warts or seborrhoeic keratoses. HPV infections in organ transplant patients have been linked with skin cancers.

Management

In children, 30–50% of plantar warts disappear spontaneously within 6 months. Hand and foot warts should be pared by a scalpel or using an emery board. This gets rid of keratotic skin and allows easier treatment. Table 27.1 shows the available treatments. Immunosuppressed patients, especially

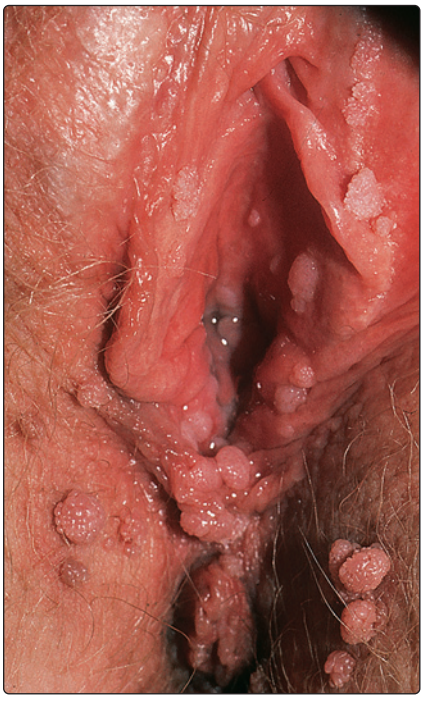


Fig. 27.3 Viral warts on the vulva.

- *Common warts*. These present as dome-shaped papules or nodules with a papilliferous surface. They are usually multiple, and are commonest on the hands (Fig. 27.1 and Fig. e27.1) or feet in children but also affect the face and genitalia. Their surface interrupts skin lines. Some facial warts are 'filiform' with fine digit-like projections.
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Viral warts can usually be managed in primary care but referral to a dermatologist is indicated if: there is diagnostic uncertainty; extensive warts or warts that have been unresponsive to conventional treatments; multiple recalcitrant warts in someone with compromised immunity; or facial warts. Patients who have warts in the anogenital area should be referred for a secondary care opinion.

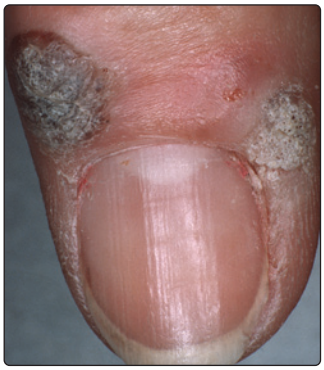
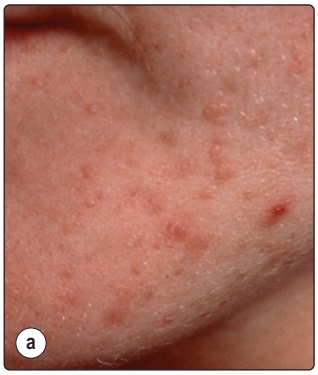


Fig. e27.1 Viral warts in a typical periungual distribution. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*



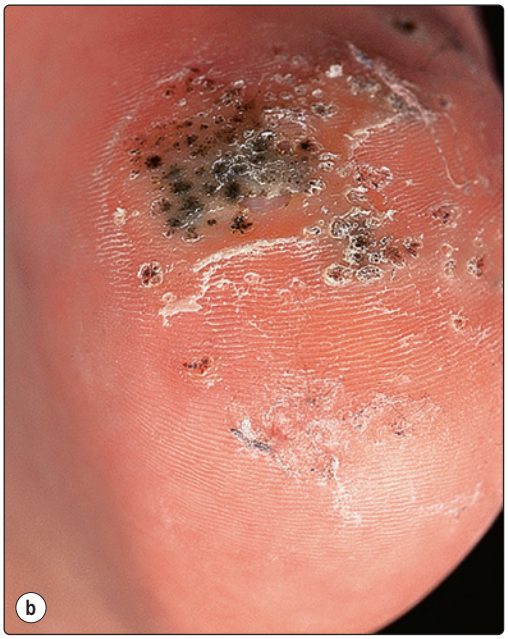


Fig. e27.2 (a) Plane viral warts on the face in a scattered distribution. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)* **(b) Mosaic plantar warts.** The black dots represent thrombosed capillaries within the wart. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

those with organ transplants, are prone to wart infections. They need special management and should be inspected and treated for warts before being given their grafts. HPV vaccine is now given to adolescent females to prevent genital tract neoplasia, especially cervical cancer.

Other viral infections

Other viral infections include molluscum contagiosum, orf, HIV (p. 58) and those in Table 27.2.

Molluscum contagiosum

Molluscum contagiosum are discrete pearly-pink umbilicated papules that are caused by a DNA pox virus. Mollusca mainly affect children or young adults. Spread is by contact, including sexual transmission or on towels. The dome-shaped papule, a few millimetres in diameter, has a punctum and, if squeezed, releases a cheesy material. The lesions are usually multiple and grouped, sometimes with a localized eczema. They are commonest on the face, neck and trunk (Fig. 27.4). Isolated ones may go unrecognized. Untreated, they may persist for several months.

If natural resolution is slow, imiquimod cream can be helpful. In the adult or older child, curettage under local anaesthesia or cryotherapy is appropriate. These measures are poorly tolerated in young children, and one approach is to instruct the parents to express the 'ripe' lesions gently after the child has been in the bath.

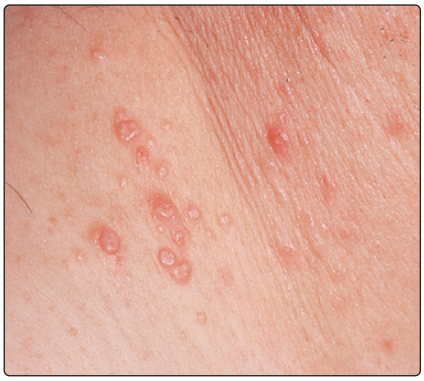


Fig. 27.4 Molluscum contagiosum on the neck.

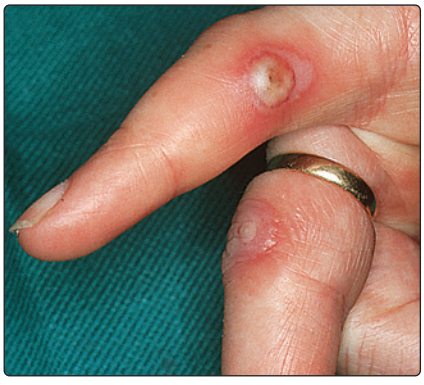


Fig. 27.5 Orf on the fingers of a farmer.

Table 27.1 **Treatments for viral warts**

Modality	Details	Indication	Contraindications/ side-effects
Topical	Salicylic and lactic acids (e.g. Duofilm, Occlusal, Salactol, Salatac)	Hand and foot warts	Facial/anogenital warts, atopic eczema, contact allergy to colophonium in collodion preparations
	Glutaraldehyde (e.g. Glutarol)	Hand and foot warts	Facial/anogenital warts, atopic eczema
	Formaldehyde (e.g. Veracur)	Foot warts	Facial/anogenital warts, atopic eczema
	Podophyllotoxin (0.15%) cream	Anogenital warts	Pregnancy (teratogenic)
	Imiquimod cream	Anogenital warts	Pregnancy; local reaction
Cryotherapy	Applied every 3–4 weeks	Hand and foot, genital warts	Painful; may cause blistering
Curettage and cautery	Local anaesthetic (or general anaesthetic if large)	Solitary filiform warts, especially on face Large anogenital warts	Not recommended for hand or foot warts as scars may result; warts may recur
Other	Intralesional bleomycin	Resistant hand/foot warts	Procedure can be painful
	Laser surgery	Any type of wart	Postoperative pain; can scar
	Interferon-β or -γ	Resistant (genital) warts	Systemic side-effects

Table 27.2 **Other viral infections**

Disorder	Cause	Clinical presentation	Course and management
Fifth disease (erythema infectiosum)	Erythrovirus (Parvovirus) B19	Slapped cheek sign, lace-like erythema over hands, feet or trunk, sometimes arthralgia	Small outbreaks typically affect children aged 2–10 years; fades in 11 days; treatment unnecessary
Gianotti–Crosti syndrome	Hepatitis B and other viruses	Small red lichenoid papules on face, buttocks and extremities	Affects young children (peak 1–12 years); clears in 2–8 weeks
Hand, foot and mouth disease	Coxsackie A16 and others	Oral blisters/ulcers, red-edged vesicles on hands/feet, mild fever	Epidemics in young children; fades in 1 week; no treatment needed
Kawasaki disease	Unknown microorganism: ? response to bacterial superantigens	Generalized erythema, peeling of hands/feet, strawberry tongue, fever, myocarditis, lymphadenopathy, coronary artery aneurysms	Affects young children; usually resolves in 2 weeks; investigate for cardiac involvement; treat with intravenous high dose immunoglobulin and aspirin
Measles	RNA morbillivirus	Koplik's spots on buccal mucosa, morbilliform rash; systemic complications possible	Incubation period 10 days, prodrome; rash fades after 6–10 days

Orf

Orf usually occurs as a solitary, rapidly growing papule, often on the hand. The orf pox virus is endemic in sheep and causes a pustular eruption around the muzzle area. Human infection is well-recognized in country regions and occurs in shepherds, veterinary surgeons and, typically, a person who has been bottle-feeding a lamb.

A solitary red papule appears, usually on a finger, after an incubation period of about 6 days (Fig. 27.5). It grows rapidly to 1 cm or so in size, evolving into a painful purple pustule, which often has a necrotic umbilicated centre. Erythema multiforme (p. 86) and lymphangitis are complications. Spontaneous resolution takes 2–4 weeks. Secondary infection requires a topical or systemic antibiotic.

Warts and other viral conditions

Viral warts

- Hand and foot warts are common: overall, 65% clear spontaneously within 2 years.
- Plane warts present as smooth flat-topped papules often on the face or dorsa of the hands.
- Try wart paints for hand and foot warts before proceeding to cryotherapy.
- Patients with anogenital warts need screening for other genital infections (p. 126).
- HPV-related anogenital dysplasias can progress to invasive carcinomas.

Molluscum contagiosum

- Caused by a pox virus. Treated by imiquimod cream, curettage or cryotherapy.
- Untreated, the lesions will remit spontaneously, although this may take several months.

Orf

- Found in rural areas, affecting farmers and vets. The condition is endemic in sheep.
- Diagnosis is usually obvious, but treat secondary infection and watch for erythema multiforme.

Molluscum contagiosum are discrete pearly-pink umbilicated papules that are caused by a DNA pox virus. Mollusca mainly affect children or young adults. Spread is by contact, including sexual transmission or on towels. The dome-shaped papule, a few millimetres in diameter, has a punctum and, if squeezed, releases a cheesy material. The lesions are usually multiple and grouped, sometimes with a localized eczema. They are commonest on the face, neck and trunk (Fig. 27.4 and Fig. e27.3). Isolated ones may go unrecognized. Untreated, they may persist for several months.

Most patients with molluscum contagiosum are children who can usually be managed in primary care on an expectant basis, as in most cases the lesions will clear spontaneously. Referral is needed when the molluscum lesions are involved around the eye (to an ophthalmologist); when the molluscum are especially widespread of problematic as in a child with coexistent atopic eczema (to a dermatologist); or in patients who have HIV (to an HIV specialist). More details on the management of viral warts and molluscum contagiosum can be found on the NHS and NICE websites (access via http://www.nhs.uk and http://cks.nice.org.uk).

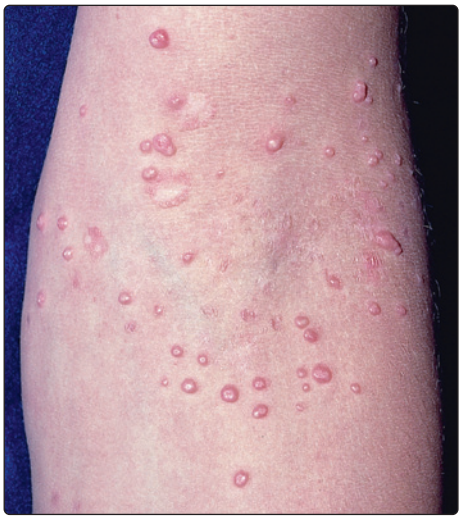


Fig. e27.3 Molluscum contagious. Numerous scattered pearly papules are evident. Some show inflammation which might indicate either secondary bacterial infection or immunological rejection. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

A solitary red papule appears, usually on a finger, after an incubation period of about 6 days (Fig. 27.5 and Fig. e27.4). It grows rapidly to 1 cm or so in size, evolving into a painful purple pustule, which often has a necrotic umbilicated centre. Erythema multiforme (p. 86) and lymphangitis are complications. Spontaneous resolution takes 2–4 weeks. Secondary infection requires a topical or systemic antibiotic.

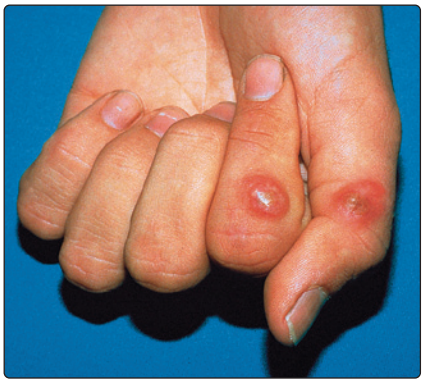


Fig. e27.4 Orf. Adjacent ('kissing') inflammatory lesions are present on the thumb and index finger. The finger lesion shows vesiculation and probably some pus formation; the vesicle on the thumb lesion has burst. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

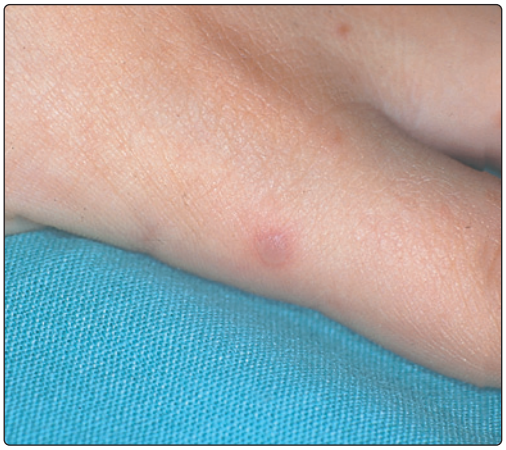


Fig. e27.5 Hand, foot and mouth disease. A typical lesion showing a small vesicle with a reddish rim. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

Table 27.2 **Other viral infections**

Disorder	Cause	Clinical presentation	Course and management
Fifth disease (erythema infectiosum)	Erythrovirus (Parvovirus) B19	Slapped cheek sign, lace-like erythema over hands, feet or trunk, sometimes arthralgia	Small outbreaks typically affect children aged 2–10 years; fades in 11 days; treatment unnecessary
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Kawasaki disease	Unknown microorganism: ? response to bacterial superantigens	Generalized erythema, peeling of hands/feet, strawberry tongue, fever, myocarditis, lymphadenopathy, coronary artery aneurysms	Affects young children; usually resolves in 2 weeks; investigate for cardiac involvement; treat with intravenous high dose immunoglobulin and aspirin
Measles	RNA morbillivirus	Koplik's spots on buccal mucosa, morbilliform rash; systemic complications possible	Incubation period 10 days, prodrome; rash fades after 6–10 days

Most cases of orf in the UK occur in farming regions where it is usually recognized by the agricultural workers, though a case might occur where, for example, a child has had contact with a sheep at a children's farm or farm park. Referral is indicated for cases where there is diagnostic difficulty or if erythema multiforme supersedes. The website of the UK Government has extensive information on orf, as it is a commercial problem in sheep farming (access via https://www.gov.uk).

Further reading – online sources

Information on viral diseases can be obtained through the NHS Choices, NICE and UK Government websites (access via http://www.nhs.uk/, http://cks.nice.org.uk/ and https://www.gov.uk/).

Further reading – textbooks

Most general large dermatological textbooks have sections on viral diseases, as do tomes on infectious disease. The following is a specialized text:

Syrjanen, K.J., Syrjanen, S.M., 2000. Papillomavirus Infection in Human Pathology. John Wiley, New York.

28 | **Viral infections** – Herpes simplex and herpes zoster

Herpes simplex

Herpes simplex is a very common, acute, self-limiting vesicular eruption due to infection with *Herpesvirus hominis*.

Aetiopathogenesis and pathology

Herpes simplex virus is highly contagious and is spread by direct contact with infected individuals. The virus penetrates the epidermis or mucous membrane epithelium and replicates within the epithelial cells. After the primary infection, the latent non-replicating virus resides mainly within the dorsal root ganglion, from where it can reactivate, invade the skin and cause recrudescent lesions. There are two types of herpes simplex virus. *Type 1* disease is usually facial or non-genital, and *type 2* lesions are commonly genital, although this distinction is not absolute. The pathological changes of epidermal cell destruction by the herpes virus result in intraepidermal vesicles and multinucleate giant cells. Infected cells may show intranuclear inclusions.

Clinical presentation

Type 1 primary infection usually occurs in childhood and is often subclinical. Acute gingivostomatitis is a common presentation in those with symptoms. Vesicles on the lips and mucous membranes quickly erode and are painful. Sometimes the cornea is involved. The illness is often accompanied by fever, malaise and local lymphadenopathy, and lasts about 2 weeks.

Herpetic whitlow is another presentation (Fig. 28.1). A painful vesicle or pustule is found on a finger in, e.g. a nurse or dentist attending a patient secreting the virus. Similar direct inoculation is sometimes seen in sportsmen such as wrestlers ('herpes gladiatorum').

Type 2 primary infection is normally seen after sexual contact in young adults, who develop acute vulvovaginitis or penile or perianal lesions. Culture-positive genital herpes simplex in a pregnant woman at the time of delivery is an indication for caesarean section, as neonatal infection can be fatal.

Recurrence is a hallmark of herpes simplex infection; it occurs at a similar site each time, usually on the lips, face (Fig. 28.2) or genitals (Fig. 28.3). Rarely, herpes simplex may appear in a zosteriform dermatomal distribution. The outbreak of groups of vesicles is often preceded for a few hours by tingling or burning. Crusts form within 24–48 h, and the infection fades after a week. Attacks may be precipitated by respiratory infection (hence 'cold' sore), sunlight or local trauma.

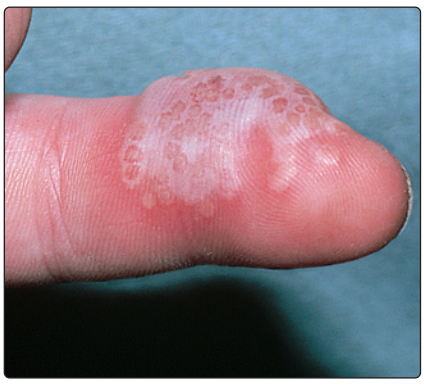


Fig. 28.1 Primary herpes simplex occurring as a herpetic whitlow on a finger.

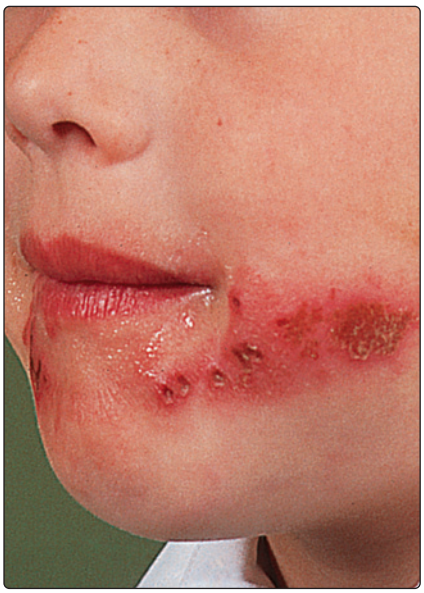


Fig. 28.2 Herpes simplex on the cheek of a child.

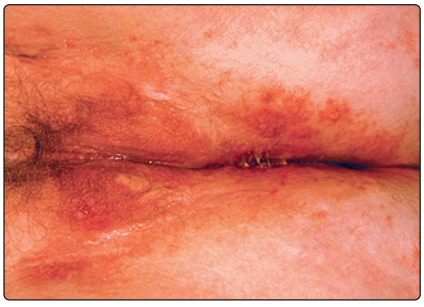


Fig. 28.3 Genital lesions of recurrent herpes simplex.

Differential diagnosis

Occasionally, herpes simplex can be confused with impetigo but, in recrudescent disease, the recurrent nature usually indicates the diagnosis. If necessary, the virus can be cultured or detected by an immunofluorescent test.

Complications

Complications are infrequent but can be serious. They include the following:

- *Secondary bacterial infection*. This is usually due to *Staphylococcus aureus*.
- *Eczema herpeticum*. Widespread herpes simplex infection is a serious and potentially fatal complication seen in patients with atopic eczema (p. 38) or Darier's disease (p. 94).
- *Disseminated herpes simplex*. Widespread herpetic vesicles may occur in the newborn or in immunosuppressed patients.
- *Chronic herpes simplex*. Atypical and chronic lesions may be seen in patients with HIV infection.
- *Herpes encephalitis*. This is a serious complication of herpes simplex, not always accompanied by skin lesions.
- *Carcinoma of the cervix*. This is more common in women with serological evidence of infection with type 2 herpes simplex, which may be a predisposing factor.
- *Erythema multiforme*. Herpes simplex infection is the most common cause of recurrent erythema multiforme (p. 86).

Management

Mild herpetic lesions may not require any medication. The treatment of choice for recurrent mild facial or genital herpes simplex is aciclovir (Zovirax) cream (applied five times a day for 5 days), which reduces the length of the attack and the duration of viral shedding, and should preferably be started at the first indication of a recrudescence. More severe episodes warrant oral treatment with aciclovir (200 mg five times a day for 5 days), which shortens the attack. Long-term oral administration is useful in those with frequent recurrent attacks. Intravenous aciclovir may be life-saving in the immunosuppressed and in infants with eczema herpeticum. Genital herpes simplex can also be treated with oral famciclovir or

Type 1 primary infection usually occurs in childhood and is often subclinical. Acute gingivostomatitis is a common presentation in those with symptoms. Vesicles on the lips and mucous membranes quickly erode and are painful (Fig. e28.1). Sometimes the cornea is involved. The illness is often accompanied by fever, malaise and local lymphadenopathy, and lasts about 2 weeks.

Recurrence is a hallmark of herpes simplex infection; it occurs at a similar site each time, usually on the lips, face (Fig. 28.2 and Fig. e28.2) or genitals (Fig. 28.3). Rarely, herpes simplex may appear in a zosteriform dermatomal distribution. The outbreak of groups of vesicles is often preceded for a few hours by tingling or burning. Crusts form within 24–48 h, and the infection fades after a week. Attacks may be precipitated by respiratory infection (hence 'cold' sore), sunlight or local trauma.

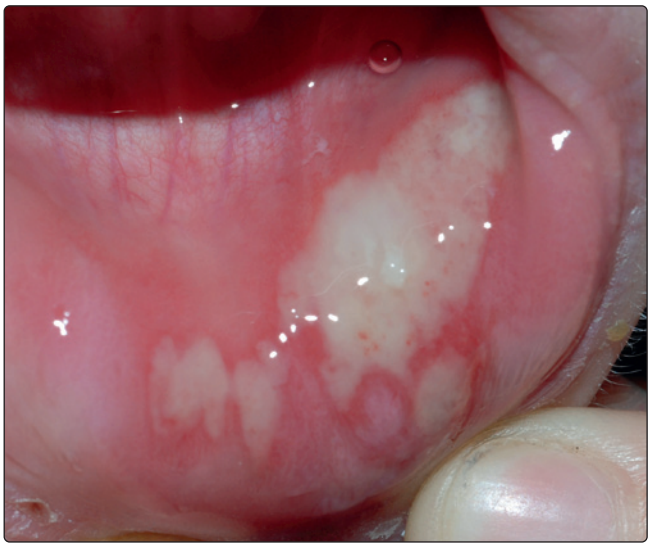


Fig. e28.1 Gingivostomatitis due to primary infection with herpes simplex in a child. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

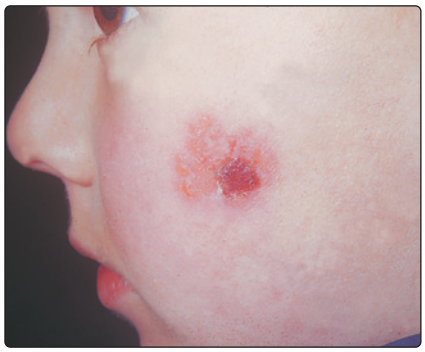


Fig. e28.2 Herpes simplex on the cheek with blistering and crusting. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

valaciclovir. In those with genital herpes simplex, barrier contraception methods are advisable during intercourse, and intercourse should be avoided during symptomatic episodes.

Herpes zoster

Herpes zoster (shingles) is an acute, self-limiting, vesicular eruption occurring in a dermatomal distribution; it is caused by a recrudescence of *Varicella zoster* virus.

Aetiopathogenesis and pathology

Herpes zoster nearly always occurs in subjects who have previously had varicella (chickenpox). The virus lies dormant in the sensory root ganglion of the spinal cord but, when reactivated, the virus replicates and migrates along the nerve to the skin, producing pain and ultimately inducing the cutaneous lesions of shingles. A viraemia is frequent, and disseminated involvement may be seen. The pathological changes are identical to those of herpes simplex.

Clinical presentation

Pain, tenderness or paraesthesia in the dermatome may precede the eruption by 3–5 days. Erythema and grouped vesicles follow, scattered within the dermatomal area (Fig. 28.4). The vesicles become pustular and then form crusts that separate in 2–3 weeks to leave scarring. Secondary bacterial infection may occur. Herpes zoster is normally unilateral and may involve adjacent dermatomes. The thoracic dermatomes are affected in 50% of cases and, in the elderly, involvement of the ophthalmic division of the trigeminal nerve is particularly common (Fig. 28.5). Two-thirds of patients with herpes zoster are over 50 years of age, and it is uncommon in children. The lesions shed virus, and contacts with no previous exposure may develop chickenpox.

Some scattering of vesicles outwith the dermatomal distribution is not uncommon, but disseminated or unusually haemorrhagic vesicles raise the possibility of immunosuppression or underlying malignancy. Local lymphadenopathy is usual, as is sensory disturbance of varying degree, including pain, numbness and paraesthesia. Shingles is recurrent in 5% of cases.

Differential diagnosis

The prodromal pain of herpes zoster can mimic cardiac or pleural pain, or an acute abdominal emergency. Once the eruption has appeared, the diagnosis is usually obvious, although herpes simplex may infrequently occur in a dermatomal fashion. Viral culture is sometimes needed.

Complications

Serious complications may occur in herpes zoster. These include the following:

- *Ophthalmic disease*. Corneal ulcers and scarring may result from shingles of the first trigeminal division. Ophthalmological assistance is mandatory.
- *Motor palsy*. Rarely, the viral involvement may spread from the posterior horn of the spinal cord to the anterior horn, and result in a motor disorder. Cranial nerve palsies or paralysis of the diaphragm or other muscle groups may occur.
- *Disseminated herpes zoster*. Immunosuppressed subjects, and patients with Hodgkin's disease in particular, can develop confluent haemorrhagic involvement, which spreads and may become necrotic or gangrenous. Varicella pneumonia or encephalitis are potentially fatal.
- *Post-herpetic neuralgia*. Neuralgia is infrequent in patients under 40 years but is found in one-third of those over 60 years. The pain subsides in the majority within 12 months.

Management

In mild shingles, treatment is symptomatic, with rest, analgesia and bland drying preparations such as calamine lotion. Secondary bacterial infection may require a topical antiseptic or antibiotic. More severe cases may be treated, if seen within 48 h of onset, with oral aciclovir (800 mg five times a day for 7 days) or famciclovir (750 mg once daily for 7 days), which promotes resolution, reduces the viral shedding time and may reduce post-herpetic neuralgia. Immunosuppressed patients often require intravenous aciclovir. Oral prednisolone, given early in the course of herpes zoster for 14 days, reduces the incidence of post-herpetic neuralgia, but must not be used if the patient is immunosuppressed. Post-herpetic neuralgia may respond to topical capsaicin (Axsain). High-potency live varicella-zoster vaccine (Zostavax) may help prevent shingles in subjects over 50 years of age.

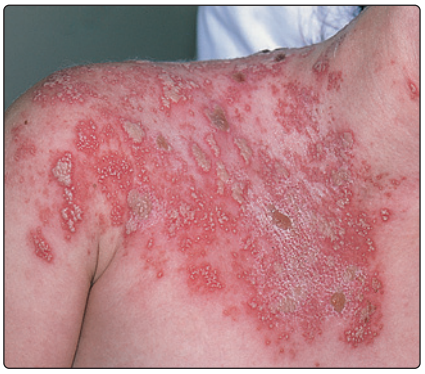


Fig. 28.4 Herpes zoster of the C4 dermatome.

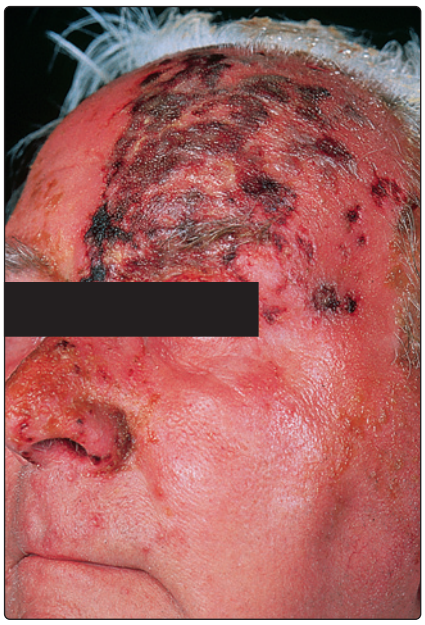


Fig. 28.5 Herpes zoster involving the ophthalmic division of the trigeminal nerve.

Herpes simplex and herpes zoster

Herpes simplex	Herpes zoster
• Type 1 infection: usually orofacial, childhood onset. Vesicles become eroded.	• Recrudescence of dormant *Varicella zoster* virus. Grouped vesicles form crusts.
• Type 2 infection: mostly genital, adult onset.	• Dermatomal, especially thoracic and trigeminal distributions.
• Characterized by recurrent bouts at the same locus.	• Neuralgia may complicate, mainly in the elderly.
• Aciclovir is an effective topical or systemic treatment.	• Dissemination suggests underlying malignancy.

Herpes zoster nearly always occurs in subjects who have previously had varicella (chickenpox, Fig. e28.3). The virus lies dormant in the sensory root ganglion of the spinal cord but, when reactivated, the virus replicates and migrates along the nerve to the skin, producing pain and ultimately inducing the cutaneous lesions of shingles. A viraemia is frequent, and disseminated involvement may be seen. The pathological changes are identical to those of herpes simplex.

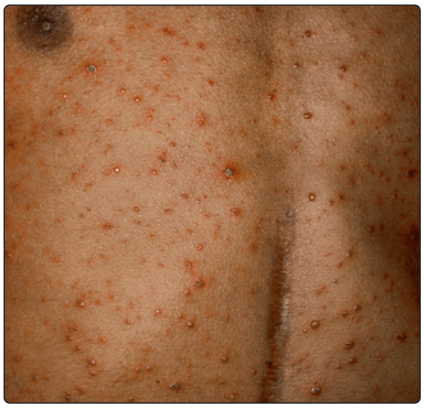


Fig. e28.3 Varicella infection (chickenpox). The widespread lesions are in different stages of development. Some are vesicular, others pustular, yet others are crusted and inflamed. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Background detail on the use of the varicella-zoster high potency live vaccine (Zostavax) is available at the US Department of Health and Human Services website (access via http://www.vaccines.gov/).

Patient self-help organizations

Patients with troublesome recurrent genital herpes simplex may be helped by the Herpes Viruses Association (www.herpes.org.uk).

Further reading – online sources

Many websites have basic information about the diagnosis and simple management of herpes simplex (e.g. http://www.webmd.com/). The US Centers for Disease Control and Prevention (CDC) has an excellent online self-learning tutorial for physicians on genital herpes simplex (accessed via http://www.cdc.gov/). The CDC website gives good additional information on herpes zoster (http://www.cdc.gov/).

Further reading – textbooks

Mindel, M., 1989, reprinted 2011. Herpes Simplex Virus. Springer-Verlag, London.

29 Human immunodeficiency virus disease and immunodeficiency syndromes

Immunodeficiency results from absence or failure of one or more elements of the immune system. It may be acquired, e.g. acquired immune deficiency syndrome (AIDS), or inherited, e.g. chronic mucocutaneous candidiasis.

Human immunodeficiency virus (HIV) disease

Infection with HIV is a progressive process that mostly leads to the development of AIDS.

Aetiopathogenesis

HIV1 and HIV2 (the latter mainly found in West Africa) are retroviruses containing reverse transcriptase, which allows incorporation of the virus into a cell's DNA. The virus infects and depletes helper/inducer CD4 T lymphocytes, leading to loss of cell-mediated immunity and opportunistic infection, e.g. with *Pneumocystis jiroveci*, mycobacteria or cryptococci. HIV is spread by infected body fluids, e.g. blood or semen. High-risk groups for HIV infection include men who have sex with men, intravenous drug users and haemophiliacs who have received infected blood products.

Clinical presentation

The acute infection may be symptomless but, in a variable proportion of cases, seroconversion is accompanied by a nonspecific glandular fever-like illness with a maculopapular exanthem on the trunk. HIV infection may be asymptomatic for several years, although most infected individuals will eventually develop symptoms. In the early stages of symptomatic infection, skin changes, fatigue, weight loss, generalized lymphadenopathy, diarrhoea and fever are present without the opportunistic infections that define AIDS. Opportunistic organisms include the ubiquitous *Mycobacterium avium* complex and *Cryptococcus neoformans*, and toxoplasmosis and cytomegalovirus.

As the disease progresses, the number of $CD4^+$ lymphocytes falls and, when the blood count is below 50 cells/mL in the late phase of HIV infection (AIDS), *M. avium* complex infection, lymphoma and encephalopathy may develop. Without treatment, the mean latent period between infection and the development of AIDS is 10 years (see Table 29.1). Skin signs include the following:

Table 29.1 A dermatologist's role in HIV infection and prompts for HIV testing

Seroconversion syndrome (often a combination of features)	Exanthem (often with mouth ulcers) Fever Myalgia Pharyngitis Headache/aseptic meningitis
Early dermatological signs	Seborrhoeic dermatitis – recalcitrant or severe Herpes zoster infection – severe, multidermatomal or recurrent Oral hairy leukoplakia (tongue) Oral candidiasis *Molluscum contagiosum* in adults Crusted scabies Severe pruritic eruptions, e.g. nodular prurigo Ulcerating herpes simplex virus
Late dermatological signs	Eosinophilic folliculitis Anal intraepithelial neoplasia Bacillary angiomatosis
AIDS-defining mucocutaneous conditions	Kaposi's sarcoma Cryptococcus/histoplasmosis of the skin (systemic infection)
Dermatological ART side-effects	Stevens–Johnson syndrome; toxic epidermal necrolysis Lipodystrophy

- *Dry skin*. Skin dryness, often with asteatotic eczema, and seborrhoeic dermatitis are common and early findings. Their severity increases as the disease advances.
- *Fungal and papillomavirus infections*. Tinea infections and perianal and common viral warts are seen in early disease.
- *Acne and folliculitis*. These worsen in early and mid-stage disease.
- *Other infections*. Oral candidiasis, oral hairy leukoplakia (thought to be associated with Epstein–Barr virus; Fig. 29.1) and infection with herpes simplex, herpes zoster, molluscum contagiosum and *Staphylococcus aureus* are increased in advanced disease.
- *Other dermatoses*. Drug eruptions, hyperpigmentation and basal cell carcinomas are more common; psoriasis can get worse and syphilis may coexist.
- *Kaposi's sarcoma*. Kaposi's sarcoma is a multicentric tumour of vascular endothelium seen in one-third of patients with AIDS or AIDS-related complex, particularly in male homosexuals. It presents as purplish nodules or macules on the face, limbs, trunk or in the mouth (Fig. 29.2), but often also involves the internal organs and lymph nodes. Kaposi's sarcoma is due to co-infection with Human Herpes Virus 8. A more benign sporadic form, seen in elderly East European Jewish men, is not associated with HIV.
- *Lymphoma*. Lymphomas seen with late-phase HIV infection are often extranodal and sometimes cutaneous.

Diagnosis

The recommended first-line diagnostic blood test identifies antibodies to HIV and p24 antigen simultaneously. These tests identify HIV from 1 month after infection, but before that, the tests may be negative. A second sample is required for confirmatory testing, HIV RNA viral load and $CD4^+$ count. Other

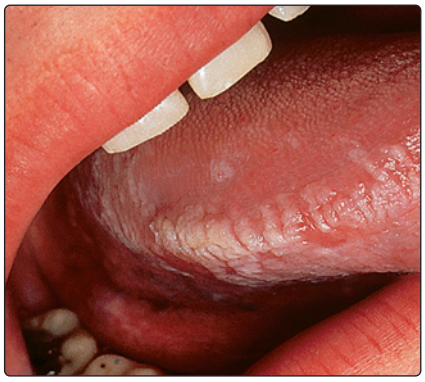


Fig. 29.1 Oral hairy leukoplakia, seen in late HIV infection (AIDS).

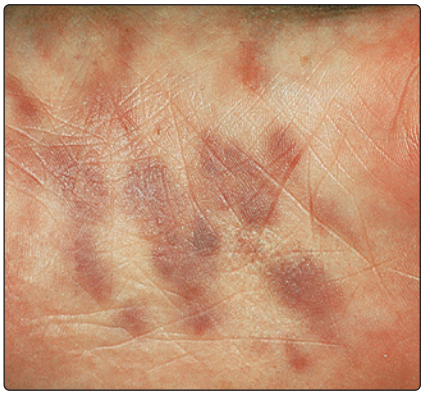


Fig. 29.2 Kaposi's sarcoma, found in intermediate and late HIV infection.

- *Dry skin*. Skin dryness, often with asteatotic eczema, and seborrhoeic dermatitis (Fig. e29.1 and Fig. e29.2) are common and early findings. Their severity increases as the disease advances.
- *Kaposi's sarcoma*. Kaposi's sarcoma is a multicentric tumour of vascular endothelium seen in one-third of patients with AIDS or AIDS-related complex, particularly in male homosexuals. It presents as purplish nodules or macules on the face, limbs, trunk or in the mouth (Fig. 29.2 and Fig. e29.3), but often also involves the internal organs and lymph nodes. Kaposi's sarcoma is due to co-infection with Human Herpes Virus 8. A more benign sporadic form, seen in elderly East European Jewish men, is not associated with HIV.

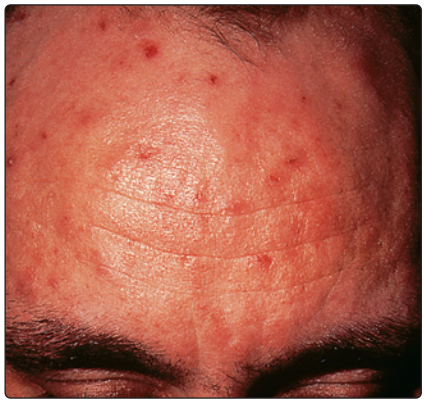


Fig. e29.1 Seborrhoeic dermatitis, often seen in early and intermediate HIV infection.

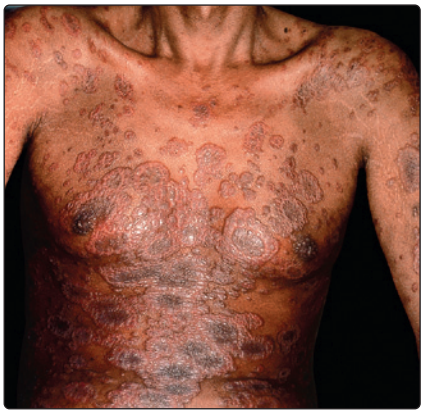


Fig. e29.2 Severe psoriasis in a patient with AIDS. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Complications of antiretroviral therapy

Antiretroviral therapy (ART) may be complicated by immune reconstitution inflammatory syndrome (IRIS) as the CD4+ count recovers. This syndrome can range from mild to severe and reflects immune responses against long-lived infections (viral, fungal, bacterial or mycobacterial). Occasionally, IRIS reactions target self-proteins in an autoimmune manner and give rise to flares in cutaneous lupus and other autoimmune diseases. Malignancies including Kaposi's sarcoma and non-Hodgkin's lymphoma are also recognized.

Additionally, ART is associated with a variety of skin adverse drug reactions. These can be specific to the individual drugs as per nucleoside/nucleotide reverse transcriptase inhibitors, or be more generalized to a class of therapy as per non-nucleoside reverse transcriptase inhibitors (Table e29.1).

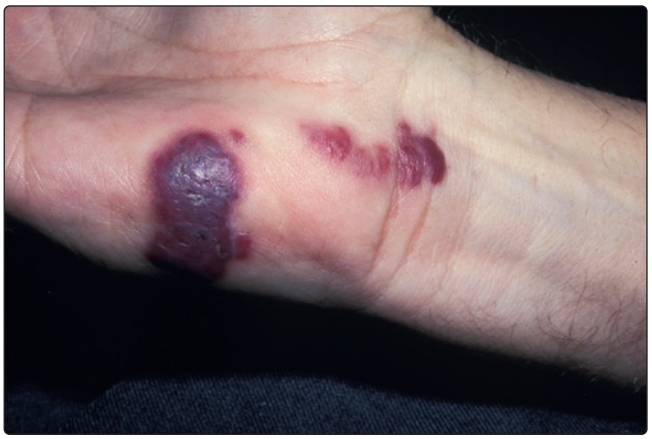


Fig. e29.3 Kaposi's sarcoma in AIDS. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Table e29.1 **HIV drug reactions**

Drug class	Drug name	Drug exanthem	DRESS/DHS	SJS/TEN	Lipodystrophy	Pancreatitis	Hepatitis	Peripheral neuropathy	Lactic acidosis	Hepatic steatosis	Increased risk of IHD	Small vessel vasculitis	Xerostomia	Myopathy	Hands/feet/mucosal hyperpigmentation	Pruritus	Xerosis	Optic neuritis	Sweets syndrome	Paronychia	Alopecia	Peripheral oedema	Renal impairment	Hypophosphataemia	Oral ulceration	Bone marrow suppression	Nausea	Cardiomyopathy	Hyperlipidaemia	Diabetes	Injection site reactions
Nucleoside/nucleotide reverse transcriptase inhibitors	Abacavir		1																1											
	Didanosine				1	1		1	1	1		1	1					1													
	Emtricitabine	1													1		1														
	Lamivudine	1				1										1				1	1										
	Stavudine				1	1		1	1	1				1								1									
	Tenofovir	1																					1	1							
	Zalcitabine	1				1		1																	1						
	Zidovudine	1			1				1	1		1			1											1	1	1			
Non-nucleoside reverse transcriptase inhibitors	Delavirdine	1	1	1			1																							
	Efavirenz	1	1	1			1																							
	Etravirine	1	1	1			1																							
	Nevirapine	1	1	1			1																							
	Rilpivirine	1	1	1			1																							
Integrase inhibitors	Raltegravir	1	1	1										1																
Protease inhibitors	Amprenavir	1		1	1		1				1		1			1												1	1	
	Atazanavir	1		1	1		1				1		1			1												1	1	
	Darunavir	1		1	1		1				1		1			1												1	1	
	Fosamprenavir	1		1	1		1				1		1			1												1	1	
	Indinavir	1		1	1		1				1		1			1												1	1	
	Lopinavir	1		1	1		1				1		1			1												1	1	
	Nelfinavir	1		1	1		1				1		1			1												1	1	
	Ritonavir	1		1	1		1				1		1			1												1	1	
	Saquinavir	1		1	1		1				1		1			1												1	1	
	Tipranavir	1		1	1		1				1		1			1												1	1	
CCR5 inhibitors	Maraviroc	1					1				1																			
Fusion inhibitors	Enfuvirtide	1																												1

SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS/DHS, drug reaction with eosinophilia and systemic symptoms/drug hypersensitivity syndrome.
(Adapted from Bolognia JL, Jorizzo JL, Schaffer JV. 2012. Dermatology, 3rd edn. Elsevier, Oxford.)

co-transmitted diseases (including syphilis and hepatitis C) and tuberculosis should be tested for. Point of care testing, from either finger prick or mouth swab samples, offers results within minutes and is increasingly available in non-healthcare settings. However, these systems currently show lower sensitivity and specificity as compared with routine laboratory tests and therefore must be confirmed with a repeat routine test.

Management

Patients should be managed by specialists in HIV disease. Infected individuals are counselled and sexual contacts are traced. Without antiretroviral therapy, 5 years after HIV infection, 15% will have progressed to AIDS, which has a high mortality, with 50% dying in 1 year and 85% in 5 years. About 20–50% of infants born to HIV-infected women have HIV disease. It is now recommended that HIV-infected individuals start antiretroviral therapy (ART) immediately at diagnosis, as this has been shown to preserve immune function, reduce morbidity and reduce the risk of onward transmission of HIV. If treated early, life expectancy can be normal. Current guidelines suggest that starting ART should include two nucleoside reverse transcriptase inhibitors (NRTIs), plus one of the following: ritonavir-boosted protease inhibitor (PI/r), non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INI). It is important to consider drug interactions between ART and other medicines, as well as herbal remedies and other over-the-counter treatments. Drug allergy reactions, including toxic epidermal necrolysis, are more common in HIV. The prophylaxis of opportunistic infection should be guided by CD4 count; <200 cells/μL requires PCP prophylaxis, but as this level drops, other pathogens need to be considered, including *Toxoplasmosis* and *Mycobacterium avium* complex (MAC). Kaposi's sarcoma may be treated with radiotherapy, cytotoxic agents or interferon-α.

Congenital immune deficiency syndromes

Congenital immune deficiency syndromes are divided into:

- *B cell deficiency*: immunoglobulin deficit; sometimes combined with …
- *T cell deficiency*: impairment of cell-mediated immunity (see p. 10).
- *Defects in effector mechanisms* such as complement or neutrophils.

Many of these conditions are very rare and present in infancy with failure to thrive. Opportunistic or pyogenic infections that often involve the skin are a feature. Examples of these include the following:

- *X-linked agammaglobulinaemia*. Infections occur in infancy once maternal antibodies run out.
- *IgA deficiency*. Affects 1 in 700 Caucasians; half have recurrent infections.
- *Severe combined immune deficiency*. Fatal in infancy because of overwhelming infection unless treated by bone marrow transplant.
- *Wiskott–Aldrich syndrome*. X-linked with T cell defects, thrombocytopenia and an associated eczema.
- *Chronic mucocutaneous candidiasis*. Seen with severe immune deficiencies, multiple endocrine dysfunction or occurring sporadically; mainly due to a T cell defect. Candidiasis usually involves the mouth, skin or nails (Fig. 29.3).
- *Chronic granulomatous disease*. Phagocytosis is defective.

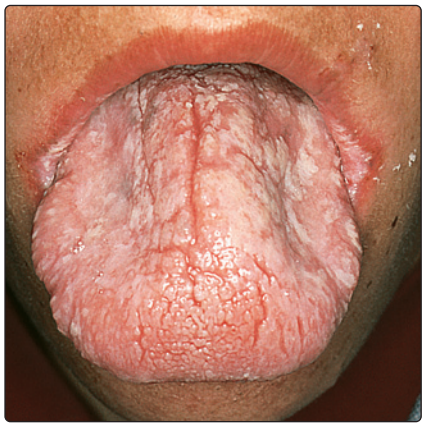


Fig. 29.3 Chronic mucocutaneous candidiasis, mainly due to a T cell defect.

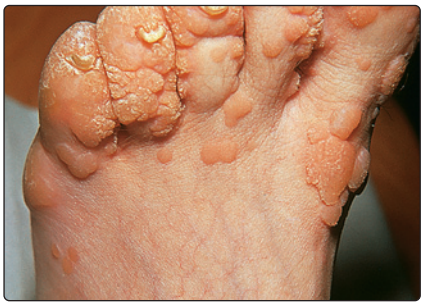


Fig. 29.4 Extensive viral warts in an immunosuppressed renal transplant patient.

Skin signs of immunosuppression for organ transplants

The use of corticosteroids, azathioprine and ciclosporin for the suppression of allograft rejection is well established. Cutaneous side-effects include not only drug eruptions and side-effects from the drugs but also infections and tumours, which develop as a result of impairment of immune surveillance, and graft-versus-host disease, which is a manifestation of an immune reaction against the host's body by the grafted tissue (p. 87). Recipients of renal allografts seem to be at particular risk of developing skin cancers. Specific skin problems in immunosuppressed allograft recipients include the following:

- *Infections and infestations*. Herpes zoster (p. 56), herpes simplex and cytomegalovirus infection may be reactivated with immunosuppressive therapy. Molluscum contagiosum, boils and cellulitis are common, and crusted 'Norwegian' scabies (p. 122) may occur.
- *Human papillomavirus infection*. About 50% of renal transplant patients have viral warts (Fig. 29.4). These may be associated with actinic keratoses or other dysplastic lesions on sun-exposed sites. The human papillomavirus acts as a carcinogen along with sun exposure.
- *Skin cancers*. The risk of skin cancer in renal transplant recipients is increased 20-fold compared with the normal population. Squamous cell carcinomas are more common than basal cell carcinomas. The tumours may look clinically and histologically banal but behave aggressively. Malignant melanoma is also more common.
- *Graft-versus-host disease*. See page 87.

HIV disease and immunosuppression

- **HIV infection** may be asymptomatic for several years. Skin signs of early HIV disease include dry skin and seborrhoeic dermatitis; signs of late disease are extensive infections, oral candidiasis and Kaposi's sarcoma. Early intervention with ART has transformed the outlook for patients with HIV.
- **Congenital immune deficiency syndromes** are rare, often present with failure to thrive in infancy and are associated with opportunistic or pyogenic infections.
- **Immunosuppression for allografts** is particularly associated with human papillomavirus infection, squamous cell carcinomas or dysplastic lesions and graft-versus-host disease.

- *Skin cancers*. The risk of skin cancer in renal transplant recipients is increased 20-fold compared with the normal population. Squamous cell carcinomas (Fig. e29.4) are more common than basal cell carcinomas. The tumours may look clinically and histologically banal but behave aggressively. Malignant melanoma is also more common.

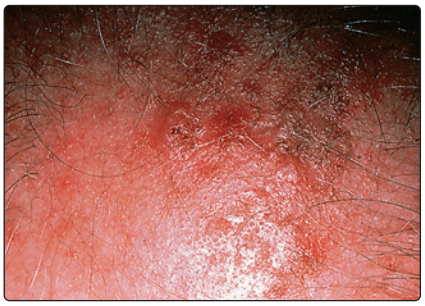


Fig. e29.4 Squamous cell carcinoma associated with immunosuppression in a renal transplant recipient.

30 Fungal infections

Fungal infection in humans is common and mainly due to two groups of fungi:

- *Dermatophytes*: multicellular filaments or hyphae.
- *Yeasts*: unicellular forms that replicate by budding.

These are usually confined to the stratum corneum, but deep mycoses invade other tissues. Yeast infections are described in Chapter 31.

Dermatophyte infections

Dermatophytes can be divided into those that spread from human-to-human (anthropophilic), animal-to-human (zoophilic) or soil-to-human (geophilic). Of these, zoophilic dermatophytes typically cause the most inflammatory reactions, which are often pustular and intensely itchy. Zoophilic dermatophytes include *Microsporum canis* (cats and dogs), *Trichophyton mentagrophytes* var. *mentagrophytes* (small mammals), and *Trichophyton verrucosum* (cattle). Anthropophilic dermatophytes cause milder, more eczematous change, which often becomes chronic and include *Trichophyton rubrum* (commonly tinea corporis), *Trichophyton tonsurans* (often scalp infections), *Epidermophyton floccosum*, *Trichophyton concentricum* and *Trichophyton mentagrophytes* var. *interdigitale*. Geophilic organisms are less common (e.g. *Microsporum gypseum*) but can cause quite inflammatory reactions.

Dermatophyte fungi reproduce by spore formation. They infect the stratum corneum, nail and hair, and induce inflammation by delayed hypersensitivity or by metabolic effects. There are three asexual genera:

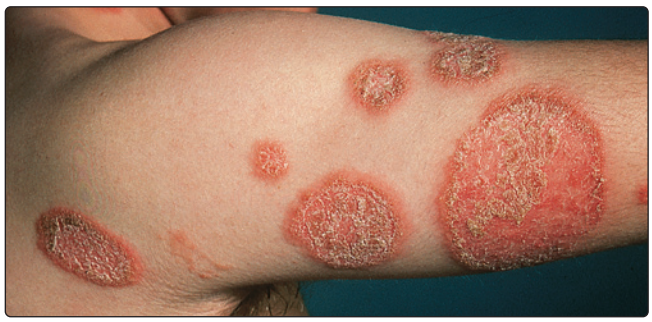


Fig. 30.1 Tinea corporis. The infection is due to animal ringworm (*T. verrucosum*) and shows intense inflammation.

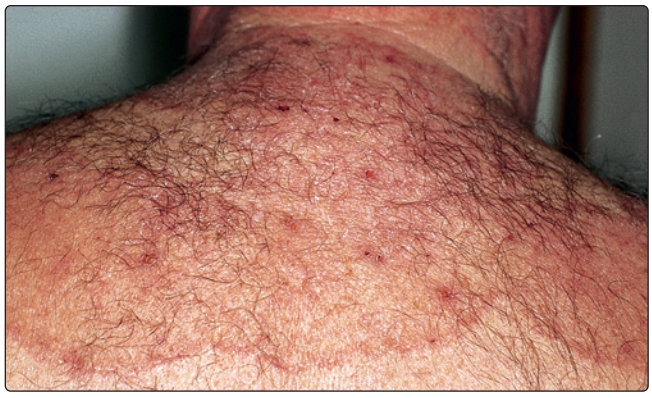


Fig. 30.2 Tinea corporis showing a well-defined edge.

- *Microsporum* infect skin and hair.
- *Trichophyton* infect skin, nail and hair.
- *Epidermophyton* infect skin and nail.

Thirty species are pathogenic in humans. Zoophilic species (transmitted to humans from animals), e.g. *Trichophyton verrucosum*, produce more inflammation than anthropophilic (human only) species.

Pathology

Dermatophytes inhabit keratin as branching hyphae, identifiable on microscopy. Skin scrapings, placed on a slide with 10% aqueous potassium hydroxide (to separate the keratinocytes) and a coverslip, are examined microscopically for hyphae (p. 21). The dermatophyte is identified by culturing the scrapings on medium (e.g. Sabouraud's) for 3 weeks.

Clinical presentation

Tinea (Latin: 'worm') denotes a fungal skin infection which is often annular. The exact features depend on the site. The various presentations include the following:

- **Tinea corporis** (trunk and limbs). Single or multiple plaques, with scaling and erythema especially at the edges, characterize this presentation. The lesions enlarge slowly, with central clearing, leaving a ring pattern, hence 'ringworm' (Fig. 30.1 and 30.2). Pustules or vesicles may be seen.
- **Tinea cruris** (groin). This is more common in men and is often seen in athletes ('jock itch'), who may also have tinea pedis. It spreads to the upper thigh but rarely involves the scrotum. The advancing edge may be scaly, pustular or vesicular. Causative organisms are shown in Table 30.1.
- **Tinea manuum** (hand). Typically, this appears as a unilateral, diffuse powdery scaling of the palm (Fig. 30.3). *Trichophyton rubrum* is often the cause. Tinea pedis may coexist.
- **Tinea incognito.** Fungal infection can be modified in appearance and spread by the antiinflammatory effect of a topical steroid (Fig. 30.4).
- **Tinea capitis** (scalp/hair) (Fig. 30.5). See p. 71.
- **Tinea unguium** (nails). See p. 72.
- **Tinea pedis** (athlete's foot) (Fig. 30.6).

Athlete's foot (Fig. 30.6) is common in adults (especially young men), rare in children and predisposed to by communal washing, swimming baths, occlusive footwear and hot weather. Itchy interdigital maceration, usually of the fourth/fifth toeweb space, is most frequent, but diffuse 'moccasin' involvement is

Table 30.1 **Superficial mycoses: causative organisms and differential diagnosis**

Area	Commonest organism	Differential diagnosis
Body/limbs (corporis)	*T. verrucosum*, *M. canis*, *T. rubrum*	Discoid eczema, psoriasis, pityriasis rosea
Feet (pedis)	*T. rubrum*, *T. interdigitale*, *E. floccosum*	Contact dermatitis, psoriasis, pompholyx, erythrasma
Groin (cruris)	*T. rubrum*, *E. floccosum*, *T. interdigitale*	Intertrigo, candidiasis, erythrasma
Hand (manuum)	*T. rubrum*	Chronic eczema, psoriasis, granuloma annulare
Nail (unguium)	*T. rubrum*, *T. interdigitale*	Psoriasis, trauma, candidiasis
Scalp (capitis)	*M. canis*, *M. audouinii*, *T. tonsurans*, *T. schoenleinii*	Alopecia areata, psoriasis, seborrhoeic eczema, furunculosis

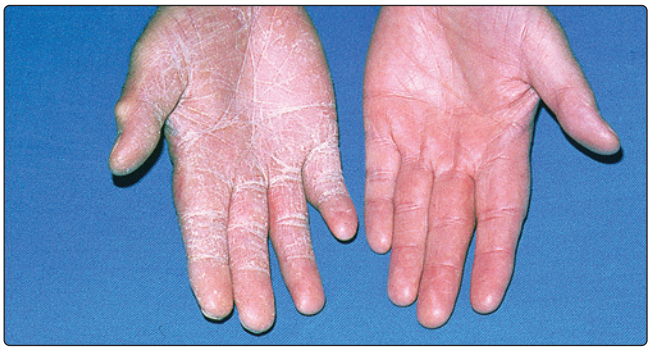


Fig. 30.3 Unilateral tinea manuum caused by *T. rubrum*.

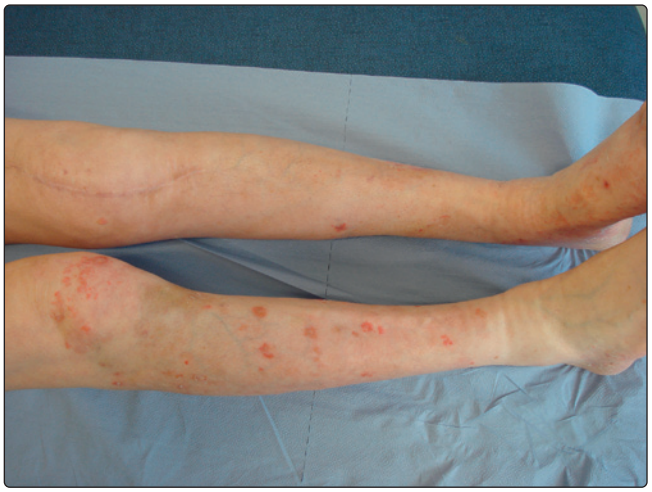


Fig. 30.4 Tinea incognito. This rash was mistakenly treated as venous eczema initially, with the application of topical corticosteroids, which led to extension of the area involved. Note the well-demarcated cut-off, which is less visible in tinea incognito.

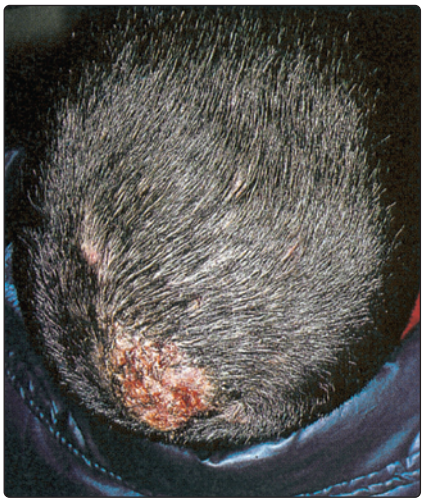


Fig. 30.5 Kerion with associated alopecia. The boggy pustular lesion results from a zoophilic dermatophyte infection.

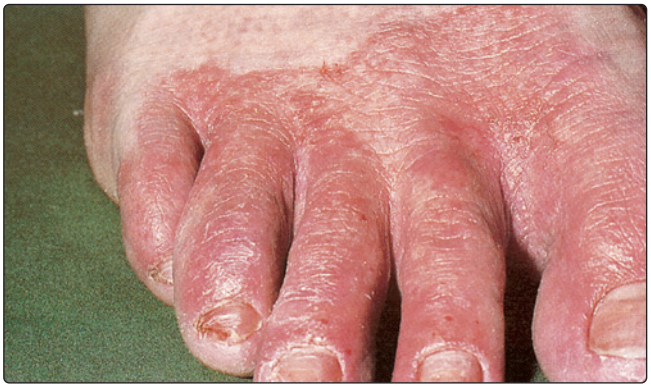


Fig. 30.6 Tinea pedis. The scaly, mildly erythematous dermatophyte infection is likely to be caused by an anthropophilic dermatophyte.

seen. Recurrent vesicles also occur, sometimes with pompholyx as an id reaction. The commonest organisms are *T. rubrum*, *T. mentagrophytes* var. *interdigitale* and *Epidermophyton floccosum*.

The differential diagnoses of superficial mycoses are shown Table 30.1. Microscopy and culture of skin scrapings are often helpful. Wood's ultraviolet light examination is used for tinea capitis, especially for screening during outbreaks. Hair infected by *Microsporum audouinii* and *M. canis* fluoresces green, but *Trichophyton tonsurans* does not fluoresce.

Management

Humid and sweaty conditions, including occlusive footwear, should be minimized, and dusting powder may help to keep the feet or body folds dry. Minor fungal infections respond to topical treatments, but widespread involvement or diseases of the nails or scalp requires systemic therapy.

Topical therapy

Tinea corporis, tinea pedis and tinea cruris respond to topical imidazole (e.g. clotrimazole and miconazole) creams, sprays or powders. Terbinafine cream once or twice daily is often effective. Amorolfine, applied once weekly, produces a 40–50% cure for tinea unguium of one or two nails; similarly ciclopirox 8% or tioconazole 28%, and the more recent Efinaconazole 10%, and tavaborole 5% solutions may be used topically.

Systemic therapy

Tinea capitis, tinea manuum, tinea unguium and extensive tinea corporis often require systemic treatment. Griseofulvin is still the licensed choice for tinea capitis in children (10 mg/kg daily for 1–2 months) but, for other indications, it has largely been superseded by the newer antifungals, terbinafine (Lamisil, often used off-licence) and itraconazole (Sporanox), which show greater efficacy, have fewer side-effects and require shorter treatments.

Terbinafine 250 mg daily or itraconazole 100 mg daily may be used for tinea capitis, corporis, cruris, manuum and pedis, given for 2–4 weeks. In tinea unguium, terbinafine (250 mg daily for 6–12 weeks) is the drug of choice; itraconazole (200 mg daily for 12 weeks or as 'pulsed' courses) is an alternative. In the elderly, uncomplicated fungal toenail infection may not require any therapy. Itraconazole can potentially cause hepatotoxicity and requires cautious use in heart failure.

Ketoconazole (Nizoral) by mouth, although effective, is limited in use by hepatotoxicity.

Fungal infections

- Dermatophytes infect the feet, groin, body, nails, hands and scalp. The commonest dermatophyte pathogens are *Trichophyton rubrum*, *T. mentagrophytes* var. *interdigitale* and *Epidermophyton floccosum*.
- Topical imidazoles and oral terbinafine or itraconazole are effective for most dermatophyte infections.
- Fungal infections covering large areas of the body or in certain sites (e.g. scalp, nails) require systemic treatment. Liver function monitoring is indicated for prolonged systemic treatment.

31 Yeast infections and related disorders

Yeasts such as *Malassezia* and *Candida albicans* exist as commensals and form a normal part of the skin microbiome, where they cause minimal inflammation in the skin. Other fungi such as dermatophytes actively digest keratin and induce significant inflammation (see Ch. 30). Yeast infections are most commonly seen in situations where the host immune system is compromised (e.g. immunosuppressive treatment, HIV).

Seborrhoeic dermatitis

Seborrhoeic dermatitis is a chronic, red, scaly, inflammatory eruption usually affecting the scalp and face (Table 31.1).

Aetiopathogenesis

Sebum production is normal, but the eruption often occurs in the sebaceous gland areas of the scalp, face and chest. Endogenous and genetic factors and an overgrowth of the commensal yeast *Malassezia* (previously *Pityrosporum ovale*) are involved. The condition is severe in some patients with HIV infection.

Clinical presentation

There are four common patterns:

1. *Scalp and facial involvement*. Excessive dandruff, with an itchy, scaly erythematous eruption affecting the sides of the nose, scalp margin, eyebrows and ears (Fig. 31.1). Blepharitis may occur. Most common in young adult males.
2. *Petaloid*. A dry, scaly patch of eczema over the presternal area.
3. *Pityrosporum folliculitis*. An erythematous follicular eruption with papules or pustules over the back (Fig. 31.2).

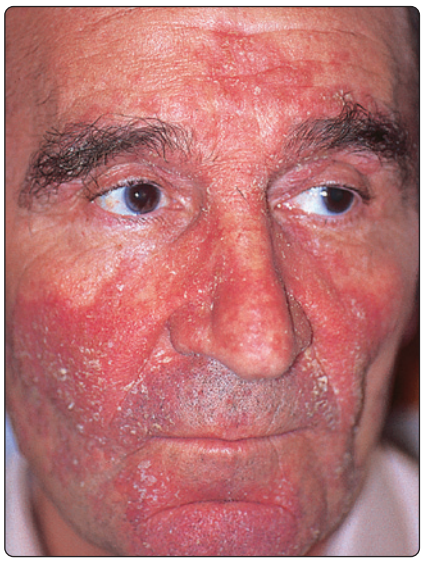


Fig. 31.1 Seborrhoeic dermatitis affecting the face.

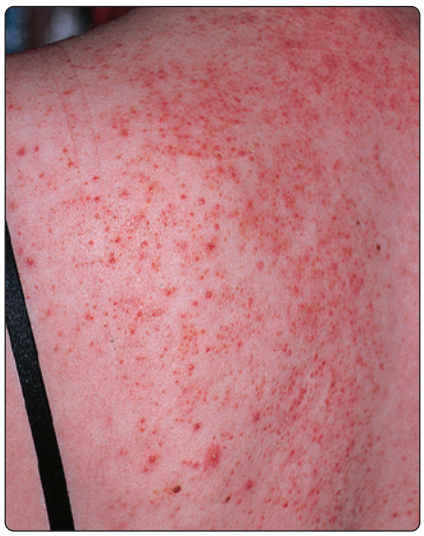


Fig. 31.2 Seborrhoeic dermatitis of the *Pityrosporum* folliculitis type affecting the back.

4. *Flexural*. Involvement of the axillae, groin and submammary areas by a moist intertrigo, often secondarily colonized by *Candida albicans*. Seen in the elderly (do not confuse with the similarly named infantile eruption, p. 120).

Management

The scalp lesions require the use of a medicated shampoo (e.g. containing coal tar, selenium sulphide or ketoconazole), either alone or following the application of 2% sulphur and 2% salicylic acid cream, left on for several hours. Facial, truncal and flexural involvement responds to an imidazole or antimicrobial, often combined with 1% hydrocortisone, in a cream or ointment base. Oral itraconazole is also effective. Recurrence is common and repeated treatment often necessary.

Pityriasis (tinea) versicolor

Pityriasis versicolor, due to the yeast *Malassezia* (previously *Pityrosporum ovale*) is a mildly scaly, inflammatory eruption usually affecting the upper chest and back, more commonly in young men (Table 31.1). Pityriasis versicolor is a chronic, often asymptomatic, fungal infection characterised by pigmentary changes and involving the trunk.

Clinical presentation

The condition is caused by overgrowth of the mycelial form of the commensal yeast *Malassezia* (previously *Pityrosporum ovale*) and is particularly common in humid or tropical conditions. In Europe, it mainly affects young adults, appearing

Table 31.1 Differential diagnosis of seborrhoeic dermatitis

Site of seborrhoeic dermatitis	Differential diagnosis
Face	Psoriasis, contact dermatitis, rosacea
Scalp	Psoriasis, fungal infection
Trunk	Psoriasis, pityriasis versicolor, fungal infection

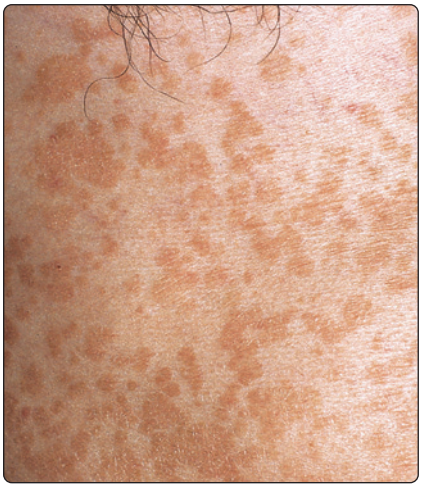


Fig. 31.3 Pityriasis versicolor on the chest. Brown scaly patches are evident.

on the trunk and proximal parts of the limbs (Fig. 31.3). In untanned, white Caucasians, brown or pinkish oval or round superficially scaly patches are seen, but, in tanned or racially pigmented skin, hypopigmentation is found as a result of the release by the organism of dicarboxylic acids that inhibit melanogenesis.

Differential diagnosis

Differentiation from vitiligo is important: usually pityriasis versicolor has a fine scale, and scrapings readily show the 'grapes and bananas' appearance of the spores and short hyphae on microscopy. Pityriasis rosea and tinea corporis may occasionally appear similar.

Management

Treatment involves either the topical application of one of the imidazole antifungals (e.g. Canesten or Daktarin cream) or the use of 2.5% selenium sulphide (Selsun) shampoo applied for 30 min (or ketoconazole [Nizoral] shampoo applied for 30 min) and showered off (use three times a week for 2 weeks). Itraconazole, 200 mg by mouth daily for 7 days, is effective for resistant cases. Recurrences are common, and patients are advised that re-treatment may be required.

Table 31.2 **Chronic mucocutaneous candidiasis**

Defect	Age of onset	Typical sites of *Candida* infection	Associated diseases
IL-17 pathway defects (including STAT1, IL-17F, IL17RA mutations, and Job's syndrome)	<2 years	Mucosae and nails	Various e.g. eczema
Autoimmune regulator (AIRE) gene defects leading to impaired T cell negative selection in the thymus	<5 years	Face and scalp	Autoimmune polyendocrinopathy, alopecia areata, vitiligo, ectodermal dystrophy
Impaired innate immune responses to yeasts due to gene mutations (e.g. CARD9, Dectin1)	Childhood	Oral and vulvovaginal	

Unknown pathways are responsible for familial chronic nail candidiasis, chronic localized candidiasis and late-onset chronic mucocutaneous candidiasis.

Candida albicans infection

Candida albicans is a ubiquitous commensal of the mouth and gastrointestinal tract that can produce opportunistic infection. Predisposing factors include:

- moist and opposing skin folds
- obesity or diabetes mellitus
- immunosuppression (Ch. 29)
- pregnancy
- poor hygiene
- humid environment
- wet work occupation
- use of broad-spectrum antibiotic.

Clinical presentation

In infection, hyphal forms of *C. albicans* are seen in the stratum corneum. Infection may present as the following:

- **Genital.** Thrush commonly appears as an itchy, sore vulvovaginitis. White plaques adhere to inflamed mucous membranes, and a white vaginal discharge may occur. Males develop similar changes on the penis. It can be spread by sexual intercourse.
- **Intertrigo.** Superinfection with *C. albicans*, and often also with bacteria, gives a moist, glazed and macerated appearance to the submammary, axillary or inguinal body folds. The interdigital clefts are involved (Fig. 31.4) in wet workers who do not dry their hands properly.
- **Mucocutaneous candidiasis.** This rare, sometimes inherited disorder of immune deficiency starts in infancy. Chronic *C. albicans* intertrigo with nail and mouth infections is seen.
- **Chronic mucocutaneous candidiasis (CMC).** CMC is a collective term for conditions which predispose to infection with *Candida albicans* because of impaired immune responses. In most cases, this reflects an underlying primary immunodeficiency (Table 31.2). Unfortunately, therapy is challenging in these cases and most patients require prolonged or long-term therapy with systemic anti-fungal medications. Correction of the underlying defect, e.g. with bone marrow transplant, may be effective.
- **Oral.** White plaques adhere to an erythematous buccal mucosa (Fig. 31.5). Broad-spectrum antibiotics, false teeth and poor oral hygiene predispose. Angular stomatitis may coexist.
- **Paronychia.** See page 72.
- **Systemic.** Systemic candidiasis can occur in immunosuppressed patients. Red nodules are seen in the skin.

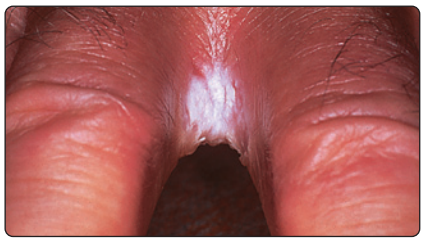


Fig. 31.4 Intertrigo of the interdigital cleft due to *C. albicans*.

Table 31.3 **Differential diagnosis: *C. albicans* infections**

Variant	Differential diagnosis
Genital	Psoriasis, lichen planus, lichen sclerosus
Intertrigo	Psoriasis, seborrhoeic dermatitis, bacterial secondary infection
Oral	Lichen planus, epithelial dysplasia
Paronychia	Bacterial infection, chronic eczema

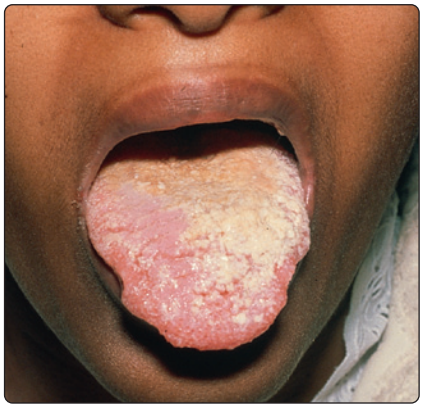


Fig. 31.5 Oral candidiasis (thrush). *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Management

Candida albicans infections must be differentiated from other conditions (Table 31.3). General measures are important. Body folds are separated and kept dry with dusting powder. Hands are dried carefully (p. 35) and oral hygiene improved. Systemic antibiotics may need to be stopped. Specific agents against *Candida* are used topically and systemically.

Topical therapy

Imidazoles are effective and available as creams, powders, pessaries and lotions. For oral candida, use amphotericin, nystatin or miconazole as lozenges, suspension or gels.

Systemic therapy

Bowel carriage may be reduced in recurrent candidiasis by oral nystatin. Itraconazole 100 mg daily or fluconazole 50 mg daily, but not griseofulvin, can be given as a short course for persistent *C. albicans* infections and in the long term, for mucocutaneous candidiasis. Vaginal candidiasis is treated by a single dose of 500 mg clotrimazole or 150 mg econazole as a pessary, or with itraconazole or fluconazole by mouth. *C. glabrata* is increasingly identified and is frequently resistant to fluconazole.

Yeast infections

- **Seborrhoeic dermatitis** commonly affects the scalp and face. It responds to combined antimicrobial/hydrocortisone creams.
- ***C. albicans*** produces opportunistic infection of the body folds, mouth, genitals and nail fold. These are predisposed to by humidity, obesity, diabetes and oral antibiotic therapy.
- **Topical imidazoles** are usually effective for candidiasis.
- **Pityriasis versicolor** is a common truncal eruption in young adults and is due to *Malassezia*, a commensal yeast. It is often revealed in the summer as pale areas adjacent to tanned skin.

32 Tropical infections and infestations

Infections constitute one of the biggest problems in dermatology in tropical countries of the developing world.

However, tropical infections may also be seen in countries in which they are non-endemic – among visitors and immigrants, or when acquired abroad by the indigenous population.

Leprosy

Leprosy is a chronic disease caused by *Mycobacterium leprae*. This is an acid- and alcohol-fast bacillus that cannot be cultured in the laboratory. Nasal droplets spread the infection, and the incubation period is several years. The disease is usually acquired in childhood, as the risk to exposed adults is about 5%. Leprosy is no longer endemic in northern Europe. Most developing countries have coordinated leprosy elimination programmes that are succeeding, but pockets of endemicity are still found in Angola, Brazil, Central African Republic, Congo, India, Madagascar, Mozambique, Nepal and Tanzania.

The manifestation of the disease depends on the degree of the delayed (type IV) hypersensitivity response in the infected individual. Those with strong cell-mediated immunity develop the tuberculoid type, whereas those in whom the cell-mediated reactivity is poor develop lepromatous leprosy. Borderline lesions are seen in those whose immune state is intermediate.

M. leprae has a predilection for nerves and the dermis but, in the lepromatous type, infection may be much more widespread. Tuberculoid leprosy is characterized by a granulomatous reaction in the nerves and dermis with no acid-fast bacilli demonstrated using the Ziehl–Neelsen stain. In contrast, bacilli are plentiful in the dermis of the lepromatous type, and large numbers of macrophages are seen on microscopy.

Clinical presentation

Tuberculoid leprosy affects the nerves and the skin. Nerves may be thickened, and anaesthesia or muscle atrophy is found. Skin lesions often occur on the face, and as few as one or two may be seen. They usually take the form of raised red plaques with a hypopigmented centre, which is typically dry and hairless (Fig. 32.1). Sensation may be impaired within the plaque.

The skin lesions of *lepromatous leprosy* are multiple and take the form of macules, papules, nodules and plaques. They are symmetrical and tend to involve the face, arms, legs and buttocks. Sensation is not impaired. Untreated, the condition is infectious from the nasal involvement. Progression gives a thickened furrowed appearance to the face (leonine facies) with loss of eyebrows (Fig. 32.2). *Borderline leprosy* shows features intermediate between lepromatous and tuberculoid.

Leprosy must be distinguished from a variety of other dermatological conditions (Table 32.1).

Complications

Tuberculoid leprosy may result in bone damage to a hand or foot from repeated trauma to an insensitive area. In lepromatous leprosy, nasal damage may progress to a saddle nose defect.

Table 32.1 **Differential diagnosis of leprosy**

Type of leprosy	Differential diagnosis
Tuberculoid	Vitiligo, pityriasis versicolor, pityriasis alba, sarcoidosis, lupus vulgaris, granuloma annulare, post-inflammatory hypopigmentation
Lepromatous	Disseminated cutaneous leishmaniasis, yaws, guttate psoriasis, discoid lupus erythematosus, mycosis fungoides

Ichthyosis, testicular atrophy and leg ulcers are seen. A peripheral neuropathy leads to shortening of the toes and fingers from repeated trauma. Lepra reactions, which result from an upgrading or a downgrading of the immune response, can produce nerve destruction or acute skin lesions.

Management

Lepromatous (multibacillary) leprosy is treated with rifampicin, dapsone and clofazimine. Treatment is for at least 2 years, continued until skin smears are negative. Tuberculoid (paucibacillary) leprosy responds to rifampicin and dapsone, given for 6 months. The complications of leprosy may require the skills of rehabilitation specialists and orthopaedic and plastic surgeons.

In countries where leprosy is endemic, education of the public about the disease is important in reducing the stigma attached to sufferers. Public health programmes aimed at leprosy control are active in several countries.

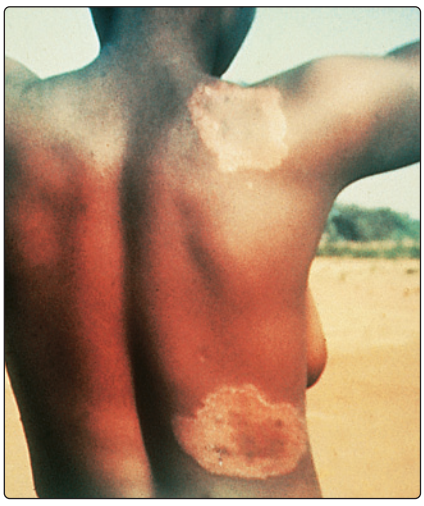


Fig. 32.1 Hypopigmented plaques of tuberculoid leprosy.

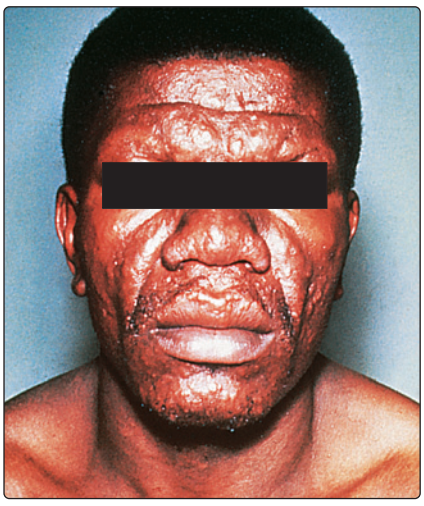


Fig. 32.2 The leonine facies of lepromatous leprosy.

Leishmaniasis

Leishmaniasis is a disease caused by *Leishmania* protozoa, which are transmitted by sand fly bites. It exists in tropical and subtropical areas in a cutaneous, mucocutaneous or visceral form. Three protozoa cause disease:

1. *Leishmania tropica* causes the cutaneous 'oriental sore' and is seen around the Mediterranean coast, in the Middle East and in Asia.
2. *L. braziliensis*, endemic in Central and South America, leads to cutaneous and mucosal disease.
3. *L. donovani* is widely distributed in Asia, Africa and South America, and

The World Health Organization has coordinated leprosy elimination programmes in developing countries. The WHO website gives good detail on how this has been achieved (access via http://www.who.int/). Lepra, an organization that is dedicated to the eradication of leprosy throughout the world, provides information on their projects (access via http://www.lepra.org.uk/).

causes visceral disease (kala-azar) with associated skin lesions.

Clinical presentation

Oriental sore is a common infection in endemic areas, normally affecting children, who subsequently develop immunity. In non-endemic regions, it is not infrequently seen in travellers after a Mediterranean holiday. The face, neck or arms are usually affected. At the site of inoculation, a red or brown nodule appears, which either ulcerates or spreads slowly to form a crust-topped plaque (Fig. 32.3). Untreated, the lesion will heal in 6–12 months, although a chronic form is seen. In *mucocutaneous leishmaniasis*, the skin lesion resembles an oriental sore but, subsequently, necrotic ulcers affect the nose, lips and palate with deformity. *Kala-azar* principally affects children and has a significant mortality. It causes hepatomegaly, splenomegaly, anaemia and debility. The cutaneous signs are patchy pigmentation on the face, hands and abdomen.

Leishmaniasis must be distinguished from some other disorders (Table 32.2).

Management

Cutaneous leishmaniasis may heal spontaneously, and small areas respond to cryotherapy. When specific treatment is needed, it is usual to give sodium stibogluconate (Pentostam) intravenously, usually for 15–21 days. The treatment for the mucocutaneous and visceral forms is similar.

Table 32.2 **Differential diagnosis of leishmaniasis**

Variant	Differential diagnosis
Cutaneous	Lupus vulgaris, leprosy, discoid lupus erythematosus
Mucocutaneous	Syphilis, yaws, leprosy, blastomycosis
Kala-azar	Leprosy

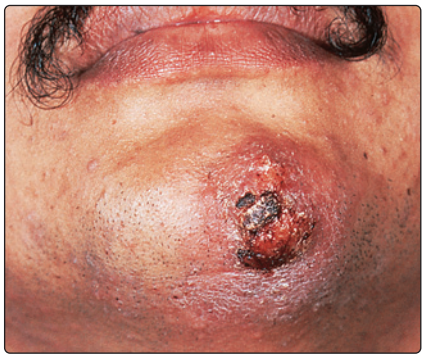


Fig. 32.3 The oriental sore of cutaneous leishmaniasis. Small lesions may respond to cryotherapy. Otherwise, intravenous sodium stibogluconate may be given.

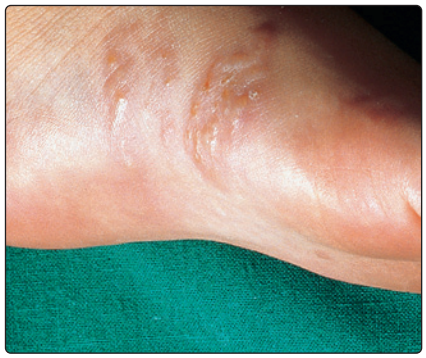


Fig. 32.4 Larva migrans seen in a child who had just visited the beaches of the West Indies. Treatment is with oral ivermectin or topical thiabendazole.

Larva migrans

Larva migrans is a 'creeping' eruption due to penetration of the skin by the larval stage of animal hookworms. Larva migrans is often acquired from tropical beaches where ova from the hookworms of dogs and cats have hatched into larvae that are able to penetrate the human skin. Penetration usually occurs on the feet. The larvae advance at the rate of a few millimetres a day in a serpiginous route causing red intensely itchy tracks to appear (Fig. 32.4). They eventually die spontaneously after a few weeks, as they cannot complete their life cycle in humans.

Topical 10% thiabendazole cream or a single oral dose of ivermectin (200 mcg/kg) is usually effective.

Deep mycoses

Deep mycoses are defined as the invasion of living tissue by fungi, causing systemic disease. Brief details are given in Table 32.3.

Table 32.3 **The deep mycoses**

Mycosis	Clinical features	Management
Actinomycosis (filamentous bacteria)	A chronic suppurating granulomatous infection with multiple sinuses discharging yellow granules, particularly around the jaw, chest and abdomen	Long-term high-dose penicillin, surgical excision
Blastomycosis	Ulcerated discharging nodules that show central clearing with scarring; may spread from pulmonary infection	Oral itraconazole, systemic amphotericin or ketoconazole
Histoplasmosis	Seen in immunosuppressed patients who develop lung disease with granulomatous skin lesions	Oral itraconazole or ketoconazole, or systemic amphotericin
Mycetoma	A chronic granulomatous infection usually of the foot, involving skin, subcutaneous tissue and bones, due to several types of fungi or actinomycetes; nodules with abscesses, sinuses, ulceration and tissue necrosis result	Depends on the organism; surgical excision, dapsone with co-trimoxazole, and itraconazole may help
Sporotrichosis	An abscess forms with nodules subsequently occurring proximally along the line of lymphatic drainage	Potassium iodide, itraconazole or terbinafine

Filariasis

Filariasis is seen in the tropics and is often due to the nematode worm *Wuchereria bancrofti*. Lymphatic damage ultimately results in gross oedema of the legs and scrotum ('elephantiasis'). Treatment is with diethylcarbamazine.

Onchocerciasis

Onchocerciasis is a disease affecting the eyes and skin, caused by the worm *Onchocerca volvulus*. It is endemic in Africa and Central America and is an important cause of blindness. A gnat transmits the worm to humans. Dermal nodules with lichenification and pigmentary change follow an itchy papular eruption. Microfilariae invade the eye and result in blindness.

Ivermectin, as a single dose, is the drug of choice for onchocerciasis. Re-treatment at 6- or 12-month intervals may be needed until the worms die out.

Tropical infections

- **Leprosy:** tuberculoid and lepromatous forms mainly affect the skin and nerves; treatment is with dapsone, rifampicin and clofazimine.
- **Leishmaniasis:** cutaneous, mucocutaneous and visceral types; treatment is with sodium stibogluconate.
- **Larva migrans:** creeping eruption due to animal hookworms; responds to thiabendazole cream or oral ivermectin.
- **Deep mycoses:** serious infections that may be difficult to eradicate.
- **Onchocerciasis:** an important cause of blindness; skin shows lichenified nodules and pigmentary changes. Treatment is with oral ivermectin.

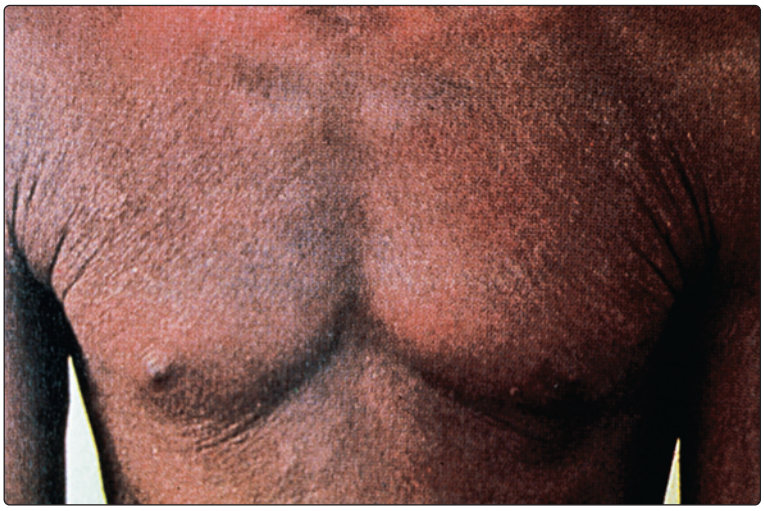


Fig. e32.1 Onchocerciasis. Lichenification and hyperpigmentation are present. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Onchocerciasis is a disease affecting the eyes and skin, caused by the worm *Onchocerca volvulus.* It is endemic in Africa and Central America and is an important cause of blindness. A gnat transmits the worm to humans. Dermal nodules with lichenification and pigmentary change follow an itchy papular eruption (Fig. e32.1). Microfilariae invade the eye and result in blindness.

Further reading – online sources

Further details on leishmaniasis and larva migrans can be found on the WHO and CDC websites (access via http://www.who.int and http://www.cdc.gov).

Additional information on the deep mycoses can be found at the CDC and the Therapeutics in Dermatology websites (access the latter via http://www.therapeutique-dermatologique.org/).

Further reading – textbooks

Tyring, S., Lupi, O., Hengge, U., 2005. Tropical Dermatology. Churchill Livingstone, Edinburgh.

Weyer, F.F., Schaller, K.F. (Eds.), 2013. Colour Atlas of Tropical Dermatology and Venereology. Springer-Verlag, Berlin.

33 Infestations

Infestation is defined as the harbouring of insect or worm parasites in or on the body. Worms – on or in the skin – are infrequent except in tropical countries. Insect life on the skin is usually transient in temperate climes, although a mite (*Demodex folliculorum*) may live harmlessly in facial hair follicles.

Insects cause a variety of skin reactions (Table 33.1). Contact with an insect or an insect bite can produce a chemical effect, such as a bee sting, or an irritant effect, such as dermatitis from contact with a caterpillar or blistering due to cantharidin released from a crushed beetle. Contact may also cause an immune-mediated response.

Insects act as vectors of skin disease, as in Lyme disease (p. 52), when animal ticks transmit *Borrelia burgdorferi*. They involve the skin directly by burrowing (e.g. scabies) or by laying eggs that hatch into larvae (myiasis).

Insect bites

The cutaneous reaction following the bite of an insect is due to a pharmacological, irritant or allergic response to the introduced foreign material.

Clinical presentation

The lesions of insect bites vary from itchy wheals (Fig. 33.1) through papules to quite large bullae (Fig. 33.2). The morphology will depend on the insect (Table 33.1) and the type of response elicited. Insect bites are usually grouped or track up a limb. Papular urticaria defines recurrent itchy urticated papules on the limbs or trunk, quite often in a child. The culprits, which may be difficult to trace, include garden insects, fleas or mites on household pets. Bedbugs cause bites on the face, neck and hands. They lie inactive in crevices in furniture during the day and emerge at night. Secondary bacterial infection of excoriated insect bites is common.

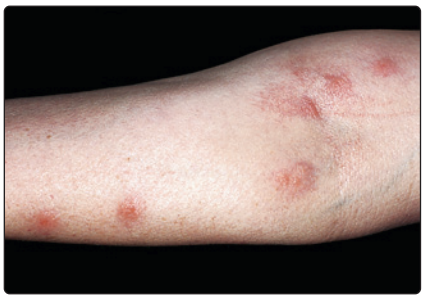


Fig. 33.1 Papular urticaria, showing grouped and linear lesions.

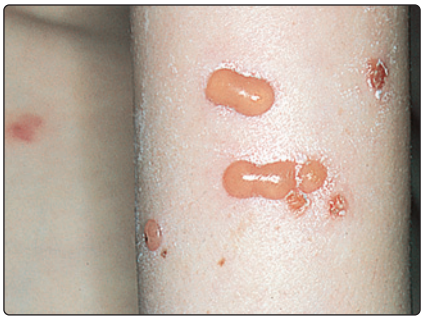


Fig. 33.2 Grouped blisters due to insect bites.

Table 33.1 **Insect effects on the skin**

Insect	Effect
Animal ticks	Bites, disease vector
Ants, bedbugs, fleas	Bites
Bees, wasps	Stings
Caterpillars	Dermatitis
Cheyletiella	Papular urticaria
Demodex folliculorum	Normal inhabitant
Food and harvest mites	Bites
Lice	Infestation (bites), disease vector
Mosquitoes	Bites, myiasis, disease vector
Sarcoptes scabiei	Scabies

Differential diagnosis

The linear or grouped nature of the lesions is usually suggestive, but sometimes urticaria, scabies, atopic eczema or dermatitis herpetiformis may need to be considered.

Management

Elimination of the cause is often not easy, as the insects are difficult to trace. Household pets must be inspected and treated if necessary. Cat fleas exist for months on carpets without a cat being present. Birds nesting or perching by a window can introduce *Cheyletiella* into a house. An individual with insect bites can be helped by crotamiton-hydrocortisone (Eurax Hc) cream or calamine lotion.

Lice infestation (pediculosis)

Lice are flat, wingless, blood-sucking insects (Fig. 33.3). Their eggs (nits) are laid on hairs or clothing. There are two anthropophilic species:

1. Pubic louse.
2. Body louse (the head louse is a variant).

Head lice are common among schoolchildren and spread by head-to-head contact. The nits are often easier to see than the lice (p. 20). The body louse is mainly seen in vagrants who live in unhygienic or poor social conditions. Spread is by infested bedding or clothing. The pubic louse is sexually transmitted and is mostly found in young adults. Lice induce intense itching which, through scratching, results in excoriation and secondary infection.

Clinical presentation

The itching of head lice usually starts at the sides and back of the scalp. Scratching results in secondary infection that may cause matted hair. Body lice result in excoriations on the trunk and, in chronic infestation, lichenification and pigmentation. The lice are found in the seams of clothes. Pubic lice, known colloquially as 'crabs', result in severe pruritus with secondary eczema and infection. They may involve the eyelashes. Lice infestation should not be confused with other conditions (Table 33.2).

Management

Head lice are treated with malathion lotion, applied to the scalp for 12 h, washed out and repeated in 7 days. Dimeticone is an alternative. Nits are removed by wet combing. Contacts are also treated. Body lice are eradicated by

Table 33.2 **Differential diagnosis of pediculosis**

Louse infestation	Differential diagnosis
Body louse	Scabies, chronic eczema
Head louse	Impetigo, eczema
Pubic louse	Scabies, eczema

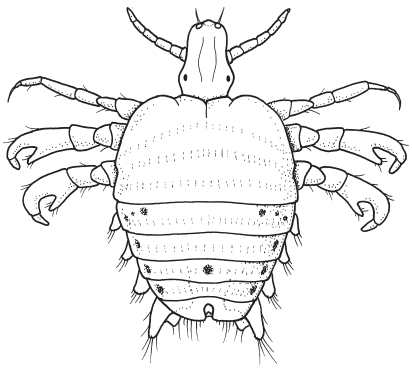


Fig. 33.3 The female pubic louse.

Insect bites can be difficult to diagnose, requiring a high index of suspicion, and it can be even more problematic on occasions to identify the causative arthropod.

treating the clothing with tumble drying, laundering or dry cleaning. Malathion or permethrin lotions may be used on the skin. Infestation with pubic lice requires the application of malathion or permethrin aqueous lotions to all the body. Sexual partners should be treated.

Scabies

The scabies mite, *Sarcoptes scabiei* var. *hominis*, is 0.4 mm in length (Fig. 33.4) and is spread by direct physical transfer, including sexual contact. The fertilized female mite burrows through the stratum corneum at the rate of 2 mm/day, laying two or three eggs each day. The eggs hatch after 3 days into larvae, which form shallow pockets in the stratum corneum where they moult and mature within about 2 weeks. The mites mate in the pockets; the male dies, but the fertilized female burrows and continues the cycle. After first being infested, it takes 3–4 weeks for the hypersensitivity reaction to the mite, and the intense itching that it causes, to develop. On average, about 12 mites are present at the itching stage, but it can be many more.

Clinical presentation

The irregular, tortuous and slightly scaly burrows measure up to 1 cm long. They are commonest on the sides of fingers (Fig. 33.5), wrists, ankles and nipples, and on the genitalia where they form rubbery nodules. Small vesicles are often seen. Itching induces excoriations (Fig. 33.6). In infants, the feet are frequently involved and the face can be affected. The mite is occasionally visible as a white dot at the end of a burrow. If extracted with a needle and viewed under a microscope, the diagnosis is irrefutable.

Scabies is often accompanied by an ill-defined eczematous urticated papular hypersensitivity reaction on the trunk. Untreated, scabies becomes chronic.

Differential diagnosis

Other intensely itchy eruptions, such as lichen planus, dermatitis herpetiformis, papular urticaria and eczema, may need to be considered, but only scabies shows burrows. Animal scabies, due to animal mites, causes an itchy eruption, but burrows are absent.

Complications

Scabies commonly becomes secondarily infected. In institutionalized or immunosuppressed patients, very large numbers of mites proliferate to produce an extensive crusted eruption known as 'Norwegian' scabies (p. 122).

Patients commonly feel itchy for some days even after adequate treatment, and pruritic non-infested 'post-scabetic' nodules may persist for weeks. Scabicides often cause an irritant dermatitis, and care must be taken to distinguish this from persistent or recurrent infestation.

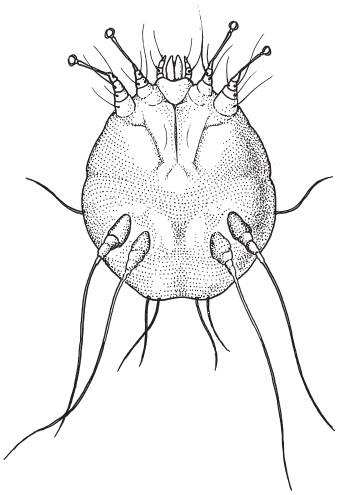


Fig. 33.4 The female scabies mite.

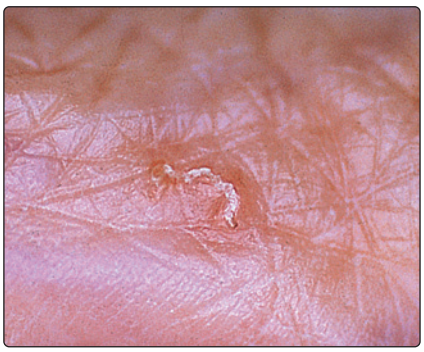


Fig. 33.5 A scabetic burrow on the side of the finger in an elderly patient.

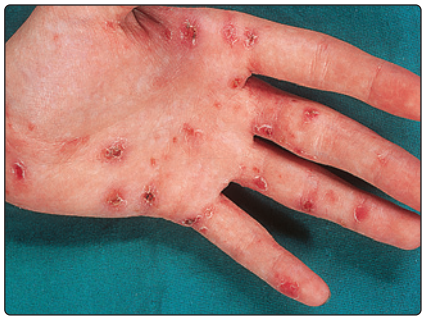


Fig. 33.6 Multiple excoriations on the hand due to scabies infestation.

Management

An adequate application technique and the treatment of all contacts are most important in the treatment of scabies. If either is lacking, persistence or re-infestation may result. An instruction leaflet for patients is helpful. The aqueous preparations of permethrin (Lyclear Dermal) and malathion (Derbac-M) are effective. Benzyl benzoate, crotamiton (Eurax) and 10% sulphur ointment are alternatives. Oral ivermectin (200 mcg/kg) two doses 1 week apart may be used when topical therapy alone is ineffective, e.g. in crusted scabies. For topical treatment, the suggested technique is as follows:

- Apply the lotion or cream to the entire body surface including scalp, face, neck and ears.
- Pay special attention to fingerweb and toeweb spaces, and under the nails.
- Leave the lotion on for 12–24 h and then wash off in the bath or shower.
- If the hands are washed during this period, re-apply the lotion or cream.
- Repeat the treatment after 1 week.

Recently infested individuals do not itch, and close contacts (such as the whole family) and sexual partners need treatment. Scabies often breaks out in old people's homes or geriatric wards and presents the problem of how far to extend the therapeutic net. The safe rule is to treat all members of a ward or home, including nurses, who have contact with the index case. Clothing and bedding is laundered. The mite dies within a few days away from the skin.

Infestations

- **Insect bites** present on the trunk and limbs as groups of itchy, often blistering, papules; secondary infection is common.
- **Head lice** infestation is transmitted between schoolchildren by head contact. Secondary infection is common. Repeated treatment is often necessary.
- **Body lice** occur in those living in poor social conditions and produce excoriation and lichenification.
- **Pubic lice** are sexually transmitted and present with pruritus and secondary infection.
- **Scabies** is spread by direct transfer and is intensely itchy. All contacts need treatment. Outbreaks are frequently seen in nursing homes where there is quite often an 'index' case with crusted scabies.

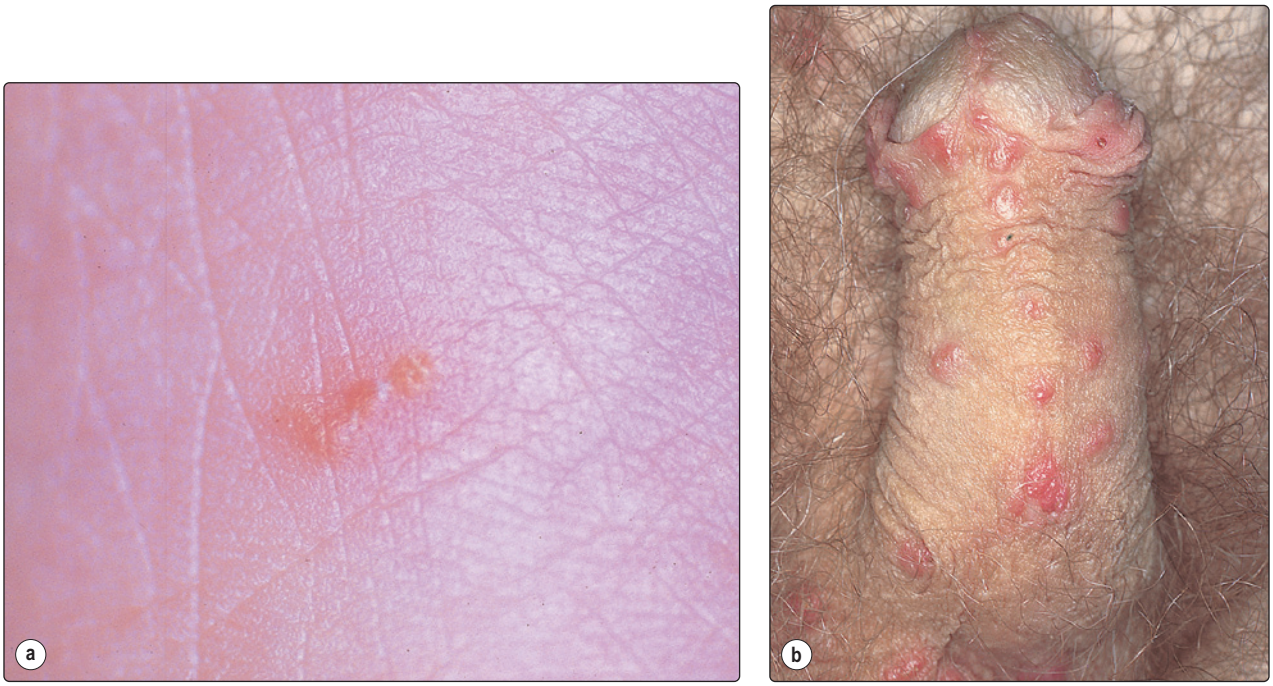


Fig. e33.1 A scabetic burrow. (a) A scabetic burrow magnified. The burrow is a few millimetres long and can be viewed with a hand lens or a dermoscope. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)* (b) Scabetic nodules on the penis. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

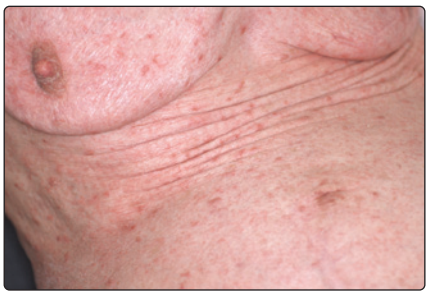


Fig. e33.2. The papular secondary eruption associated with scabies. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

Head lice have become very common again in school children and outbreaks are frequent, so that many parents are familiar with the self-treatment of the problem. Re-infestation is not uncommon. Excellent details on the life cycles and management of lice and problems with insect bites can be accessed through the Centers for Disease Control and Prevention website (access via http://www.cdc.gov/).

The scabies mite is related phylogenetically to the house-dust mite.

The irregular, tortuous and slightly scaly burrows measure up to 1 cm long. They are commonest on the sides of fingers (Fig. 33.5 and Fig. e33.1a), wrists, ankles and nipples, and on the genitalia where they form rubbery nodules (Fig. e33.1b). Small vesicles are often seen. Itching induces excoriations (Fig. 33.6). In infants, the feet are frequently involved and the face can be affected. The mite is occasionally visible as a white dot at the end of a burrow. If extracted with a needle and viewed under a microscope, the diagnosis is irrefutable.

Scabies is often accompanied by an ill-defined eczematous urticated papular hypersensitivity reaction on the trunk (Fig. e33.2). Untreated, scabies becomes chronic.

Scabies is one of the great mimickers in dermatology, especially so in its early stages when there is itching but when the characteristic burrows are not evident. Good detail about the natural history of scabies, notably the life cycle of the mite can be found on the CDC website (access via http://www.cdc.gov/).

Oral ivermectin is being used increasingly to manage outbreaks of scabies in institutions. It is easier to administer compared with topical malathion and might be slightly more effective (though the efficacy of topical treatment may well depend on whether or not it was applied correctly). The NICE and CDC websites have useful information on treatment and the management of the infestation (access via http://cks.nice.org.uk and http://www.cdc.gov/).

Further reading – online sources

More information can be obtained via the CDC and NICE websites (access via http://www.cdc.gov and http://cks.nice.org.uk).

Further reading – textbooks

Alexander, J.O'D., 1984. Arthropods and Human Disease. Springer-Verlag, Berlin. (although published some years ago, this is a masterful and detailed text on the subject).

34 Sebaceous and sweat glands – Acne, rosacea and other disorders

Acne

Acne is a chronic inflammation of the pilosebaceous units, producing comedones, papules, pustules, cysts and scars. It affects nearly every adolescent. Acne has an equal sex incidence and tends to affect women earlier than men, although the peak age for clinical acne is 18 years in both sexes. Acne results from:

- increased sebum excretion – seborrhoea (greasy skin)
- pilosebaceous duct hyperkeratosis and comedone formation
- colonization of the duct with *Propionibacterium acnes*
- release of inflammatory mediators (including cytokines).

In acne, the androgen-sensitive pilosebaceous unit (p. 4) shows a hyper-responsiveness that results in increased sebum excretion. Factors in sebum induce comedones, and *P. acnes* initiates inflammation through chemical mediators inducing enzymes (e.g. lipase) and prostaglandins (see online for diagram).

Clinical presentation

Comedones are either open (blackheads: dilated pores with black plugs of melanin-containing keratin) or closed (whiteheads: small cream-coloured, dome-shaped papules). They appear at about the age of 12 years and evolve into inflammatory papules (Fig. 34.1), pustules or cysts (Fig. 34.2). The sites of predilection – the face, shoulders, back and upper chest – have many sebaceous glands. The severity of acne depends on its extent and the type of lesion, with cysts being the most destructive.

Acne usually persists until the early twenties, although in a few patients, particularly women, the disease continues into the fifth decade. Scars may follow healing, especially of cysts or abscesses. Scars may be 'ice-pick', atrophic (Fig. 34.3) or keloidal.

Some variants of acne are seen:

- *Acné excoriée*: due to squeezing and picking, often affects depressed or obsessional young women.
- *Chloracne*: caused by systemic toxicity of certain aromatic halogenated industrial chemicals (p. 133.e1).

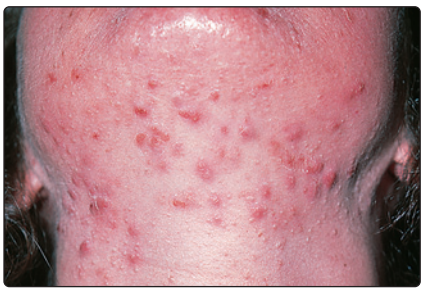


Fig. 34.1 Papular–pustular acne of the chin, with some whiteheads.

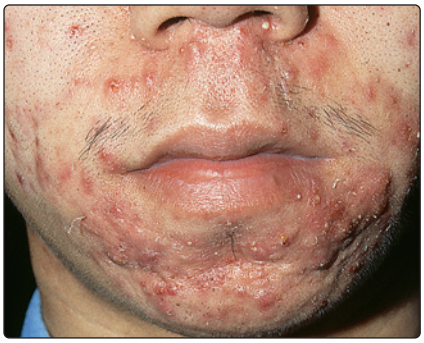


Fig. 34.2 Pustulocystic acne on the face.

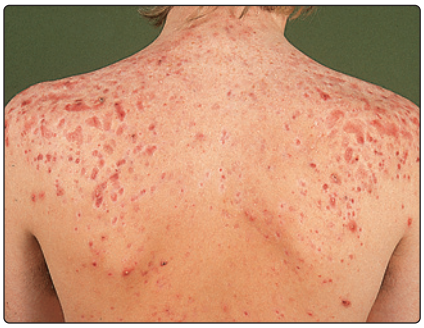


Fig. 34.3 Scarring acne on the back.

- *Conglobate*: a mass of burrowing abscesses and sinuses with scarring.
- *Cosmetic*: pomade and cosmetic-induced comedonal and papular acne (mainly seen in the United States).
- *Drug-induced*: by systemic steroids, androgens and topical steroids.
- *Infantile*: mostly found on the faces of male infants; cause unknown.
- *Physical*: occlusion by the back of a wheelchair or on a violinist's chin.

Complications and differential diagnosis

Embarrassment, social withdrawal and depression are important sequelae of acne. These can improve with effective treatment. The rare and severe acne fulminans, seen in adolescent males, is associated with fever, arthritis and vasculitis. Long-term antibiotic treatment may induce a Gram-negative folliculitis.

Rosacea can usually be differentiated from acne (see below). Bacterial folliculitis is more acute than acne, but the two may coexist.

Management

Treatment depends on the type and extent of acne and the patient's psychological state. 'Over-the-counter' creams have often already been used. Scoring the acne severity is useful (see online for details).

Local treatment is adequate for mild acne and is used with systemic drugs for more severe cases.

- *Benzoyl peroxide* (PanOxyl, Brevoxyl) cream or gel, applied twice a day, works by reducing the number of *P. acnes*. It may cause irritation, contact allergy and bleach clothing.
- *Isotretinoin* (Isotrex Gel) is good at reducing the number of comedones, but may be irritant.
- *Antibiotics*, e.g. clindamycin alone (Dalacin T) or with benzoyl peroxide (Duac Once Daily), erythromycin alone (Stiemycin) or with zinc (Zineryt), can be used for mild or moderately severe acne.
- *Other topical agents*, e.g. azelaic acid, nicotinamide and adapalene.

Oral treatment with antibiotics, retinoid or hormones is prescribed for moderate or severe acne, acné excoriée and in depressed patients.

Antibiotics

The first-line systemic antibiotic drug is oxytetracycline, 500 mg twice daily (taken 30 min before food, with water), given for a minimum of 4 months. Tetracyclines are contraindicated in children and in pregnancy, and may cause *Candida albicans* infection or photosensitivity. Lymecycline (Tetralysal, 408 mg daily) and doxycycline (Vibramycin, 100 mg once daily) are alternative tetracyclines that are better absorbed.

Erythromycin (500 mg twice daily) and trimethoprim are second-choice

Aetiopathogenesis

Acne is caused by an interaction of androgenic action on the sebaceous gland (such as increased sebum production), colonization with the bacterium *Propionibacterium acnes*, the effects of the local release of inflammatory mediators (e.g. cytokines, prostaglandins) and resultant microanatomical changes in the pilosebaceous unit (e.g. ductal hyperkeratosis). These changes are shown in Fig. e34.1.

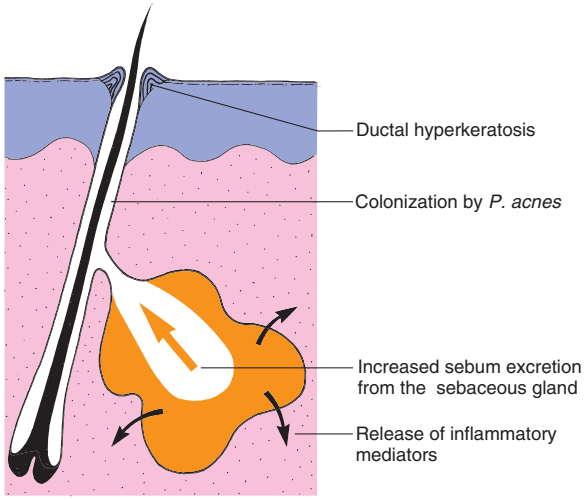


Fig. e34.1 The aetiopathogenesis of acne.

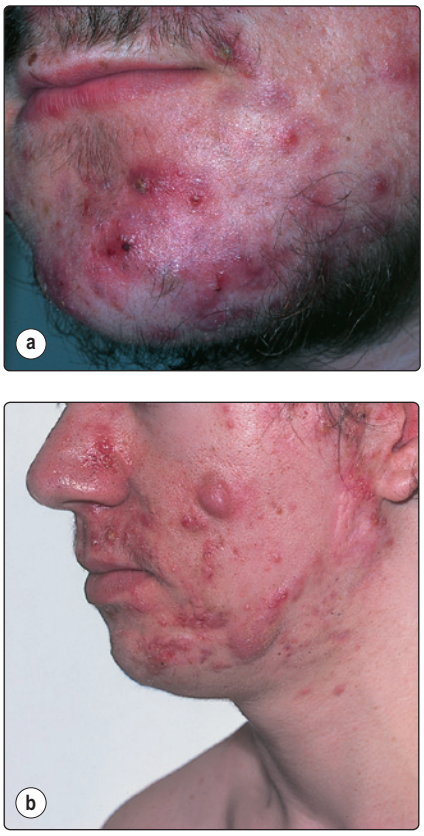


Fig. e34.2 Inflammatory acne.
(a) Inflammatory acne with pustules (and some papules and comedones) on the face. (b) Facial acne with large cysts. Large cysts may require drainage and the injection of triamcinolone acetonide. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

Comedones are either open (blackheads: dilated pores with black plugs of melanin-containing keratin) or closed (whiteheads: small cream-coloured, dome-shaped papules). They appear at about the age of 12 years and evolve into inflammatory papules (Fig. 34.1), pustules or cysts (Fig. 34.2 and Fig. e34.2). The sites of predilection – the face, shoulders, back and upper chest – have many sebaceous glands. The severity of acne depends on its extent and the type of lesion, with cysts being the most destructive.

Grading the severity of acne

The treatment of acne needs to be tailored to the needs of the patient. Pre-treatment assessment of the patient requires the doctor to establish the severity of the acne in addition to taking into account previous treatments, lifestyle factors and the psychological impact that acne has had on the individual. Although acne might be regarded as mild if there were 'only' comedones with a few scattered papules and pustules, moderate if there were papules and pustules and severe if nodules and cysts were present, it is helpful to have a more robust scoring system. The impact of acne on an individual can be measured using the Assessment of the Psychological and Social Effects of Acne (APSEA) questionnaire (access through the Medscape website, via http://www.medscape.com/).

The physical lesions of acne can be graded by several methods. A commonly used system in Europe is the Leeds one, which can be accessed online (access under 'forms' via http://carepathways4gp.org.uk/). It has multiple illustrative photographs, grading the face, chest and back. Other grading protocols can be used (search 'scoring systems in acne vulgaris', access via http://www.bioline.org.br/ and on the FDA website, access under 'acne global severity scale', via http://www.fda.gov/default.htm). The individual's view of the severity of their acne is often different from the doctor's objective one and this needs to be recorded.

Rare syndromes associated with acne

An uncommon multisystem condition in which there is pyogenic arthritis, pyoderma gangrenosum and acne (named 'PAPA' syndrome) has been recognized. It is one of a newly recognized group of diseases known as '*autoinflammatory syndromes*', some of which have a genetic basis. The disease combination characterized by pyoderma gangrenosum, acne and hidradenitis supportiva (PASH) and SAPHO syndrome (in which there is synovitis, acne, pustulosis, hyperostosis and osteitis) are other examples. Interleukin-1β is involved in the causation of these diseases.

Guidance on how to treat acne is available from the NICE website (access via http://cks.nice.org.uk/).

antibiotics. Women on oral contraceptives who take an antibiotic are advised that, if diarrhoea develops, additional contraception is needed for the rest of the menstrual cycle.

Antiandrogen

The combination of an antiandrogen and an oestrogen (co-cyprindiol–cyproterone acetate, 2 mg, and ethinylestradiol, 35 mcg: Dianette) is used in females (not males) with moderate to severe acne that is resistant to conventional therapy. The antiandrogen suppresses sebum production. Co-cyprindiol is given for 6–12 months and is also a contraceptive.

Retinoid

Isotretinoin (Roaccutane), which reduces sebum excretion, inhibits *P. acnes* and is antiinflammatory, is a very effective treatment for acne. It is used if acne is severe or unresponsive to conventional treatment, or if acne relapses quickly once antibiotics are stopped. A course lasts 4 months and requires the monitoring of liver function and fasting lipids. Isotretinoin is teratogenic. Women given the drug must not be pregnant and need to take the oral contraceptive throughout treatment and for the month before and after. Side-effects include cracked lips, dry skin, nose bleeds, hair loss, muscle aches and mood change.

Other therapies

Acne cysts may require injection with triamcinolone acetonide (a steroid), or sometimes excision or cryotherapy. Comedones can be removed using an extractor. Diet has no effect on acne.

Rosacea

Rosacea is a chronic inflammatory facial dermatosis characterized by erythema and pustules. The cause of rosacea is unknown. Histologically, dilated dermal blood vessels, sebaceous gland hyperplasia and an inflammatory cell infiltrate are seen. Sebum excretion is normal.

Clinical presentation

Rosacea has an equal sex incidence. Although commonest in middle age, it also affects young adults and the elderly. The earliest symptom is flushing. Erythema, telangiectasia, papules, pustules (Fig. 34.4) and, occasionally, lymphoedema, involve the cheeks, nose, forehead and chin. Rhinophyma, hyperplasia of the sebaceous glands and connective tissue of the nose (Fig. 34.4), and eye involvement by blepharitis and conjunctivitis are complications. Sunlight and topical steroids exacerbate the condition. Rosacea persists for years, but usually responds well to treatment. Rosacea lacks the comedones of acne and occurs in an older age group. Contact dermatitis, photosensitive eruptions, seborrhoeic dermatitis and lupus erythematosus often involve the face but are more acute or scaly, or lack pustules.

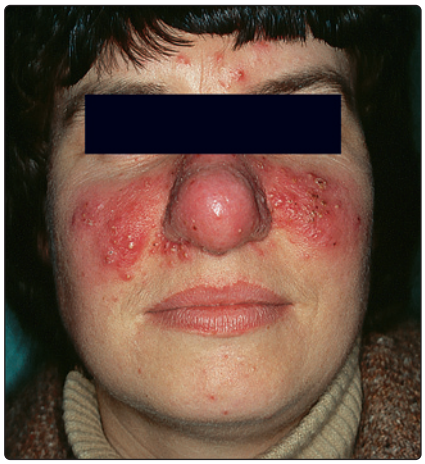


Fig. 34.4 Rosacea with rhinophyma in a woman. Rhinophyma usually affects men.

Management

Topically, metronidazole 0.75% cream, azelaic acid cream or brimonidine gel may be helpful. If this is ineffective, the usual oral treatment is oxytetracycline, initially 1 g daily, reducing to 250 mg daily after a few weeks and continued for 2–3 months. Erythromycin is an alternative. Repeated treatment is often needed. Isotretinoin can be used but is less effective than in acne. Plastic surgery or laser is required for rhinophyma.

Other disorders

Perioral dermatitis is characterized by papules and pustules that may occur around the mouth and chin of a woman who has used topical steroids. They will clear with steroid cessation and oral tetracycline therapy.

Hidradenitis suppurativa is an unpleasant chronic inflammatory condition of the infundibulum of hair follicles in the apocrine sweat gland areas of the axillae, groin and perineum. Nodules, abscesses, cysts and sinuses form, and scarring results (Fig. 34.5). Conglobate acne may coexist. Treatment is difficult. Topical antiseptics can be tried with a prolonged course of oral *clindamycin* and *rifampicin*, or the retinoid acitretin. Localized surgical excision is an option. *Infliximab* infusion has been shown to be effective in severe cases.

Hyperhidrosis (excess sweating), due to eccrine gland overactivity, is usually emotional in origin. A 20% aluminium chloride in alcohol is often effective. Iontophoresis is used for hands (p. 23.e1) and Botox injection for axillae (p. 119).

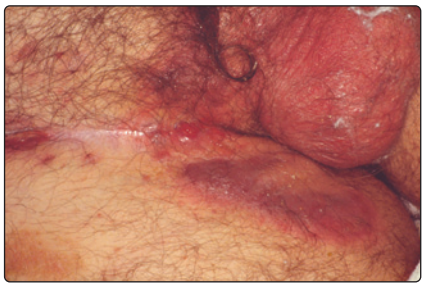


Fig. 34.5 Hidradenitis suppurativa. Multiple inflammatory nodules are evident. Scarring is common.

Sebaceous and apocrine disorders

Acne

- *Due to* increased sebum excretion, comedone formation, *P. acnes* and inflammation.
- *Presentation*: comedones, pustules, cysts and scars seen over the face, chest and trunk.
- *Treatment*: topical treatments include benzoyl peroxide and isotretinoin; systemic treatments include antibiotics, e.g. tetracyclines or erythromycin, co-cyprindiol and isotretinoin.

Rosacea

- *Affects* the middle-aged or elderly. Often starts with facial flushing.
- *Presentation*: facial erythema, telangiectasia and pustules; rhinophyma and conjunctivitis.
- *Treatment*: topical metronidazole 0.75% cream, oral oxytetracycline.

Hidradenitis suppurativa

- *Presentation*: chronic nodules or abscesses of axillae and groin, resulting in scarring.
- *Treatment*: local antiseptics, prolonged course of oral antibiotic or retinoid, excision.
- Severe cases: infliximab infusion may be appropriate for selected patients.

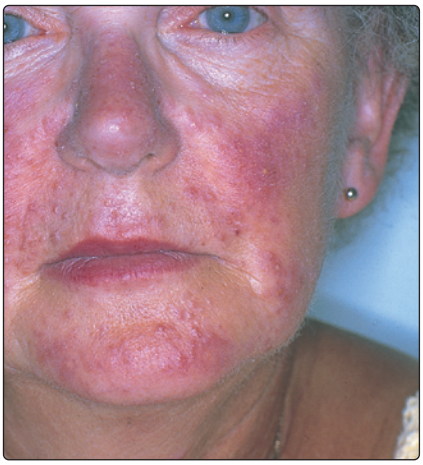


Fig. e34.3 Rosacea showing erythema and papules. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

The cause of rosacea is still unknown although it is recognized that dysregulation of the innate immune system, overgrowth of commensal organisms (Demodex mites in hair follicles) and aberrant neurovascular signalling seem to be involved.

Rosacea has an equal sex incidence. Although commonest in middle age, it also affects young adults and the elderly. The earliest symptom is flushing. Erythema, telangiectasia, papules, pustules (Fig. 34.4 and Fig. e34.3) and, occasionally, lymphoedema, involve the cheeks, nose, forehead and chin. Rhinophyma, hyperplasia of the sebaceous glands and connective tissue of the nose (Fig. 34.4) and eye involvement by blepharitis and conjunctivitis are complications. Sunlight and topical steroids exacerbate the condition. Rosacea persists for years, but usually responds well to treatment. Rosacea lacks the comedones of acne and occurs in an older age group. Contact dermatitis, photosensitive eruptions, seborrhoeic dermatitis and lupus erythematosus often involve the face but are more acute or scaly, or lack pustules.

Topical ivermectin (10 mg/g) cream (Soolantra) has been approved as a once daily treatment for inflammatory papulopustular rosacea (presumably having an effect on the Demodex population). Re-treatment is necessary after 4 months.

Perioral dermatitis is often regarded as a form of rosacea.

Intravenous infusion of infliximab has been very helpful in the management of hidradenitis suppurativa unresponsive to other therapies (see http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1025&html=1). Insulin resistance has been found in patients with hidradenitis suppurativa. Treatment with metformin may be worth considering but needs further evaluation.

Excessive generalized sweating for which systemic causes have been eliminated can be managed with oral propantheline, 15 mg three times a day. The injection of *botulinum toxin A* (Botox, Dysport) into the axillary or palmar skin will control excessive sweating in these areas, but needs to be repeated every 9 months. A new potentially permanent second-line treatment, delivered by a microwave energy device ('miraDry') under local anaesthesia targeted to the axillae, has been described for use in adults with hyperhidrosis. ℞

Patient self-help organizations

The Acne Support Group (www.stopspots.co.uk) and Changing Faces (https://www.changingfaces.org.uk/) provides support to acne sufferers. Patients with rosacea may be helped by the support group (http://rosacea-support.org/).

Further reading – online sources

Detailed information can be obtained through the NICE website (access via http://cks.nice.org.uk).

The topic of the treatment of rosacea has recently been reviewed (see Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part II 2015. Topical and systemic therapies in the treatment of rosacea. J Am Acad Dermatol 72:761–770.

Further reading – textbooks

Marks, R., 2006. Facial Skin Disorders. Taylor & Francis, Abingdon.
Zouboulis, C.C., Katsambas, A.D., Kligman, A.M., 2014. Pathogenesis and Treatment of Acne and Rosacea. Springer, Berlin.

35 Disorders of hair

Hair loss (alopecia)

The division of alopecia into diffuse, localized and scarring or non-scarring helps in diagnosis (Table 35.1). Hair loss from whatever cause (and also excessive hair) can result in psychological distress in both sexes.

Table 35.1 **Causes of hair loss**

Type of hair loss	Causes
Diffuse non-scarring	Male pattern/female pattern, hypothyroid, hypopituitary, hypoadrenal, drug-induced, iron deficiency, telogen and anagen effluvium, diffuse alopecia areata
Localized/non-scarring	Alopecia areata, ringworm, traumatic, hair pulling, traction, secondary syphilis
Localized/diffuse scarring	Burns, radiation, shingles, kerion, tertiary syphilis, lupus erythematosus, morphoea, pseudopelade, lichen planus

Diffuse non-scarring alopecia

With diffuse non-scarring alopecia, patients usually notice excessive numbers of hairs on the pillow, brush or comb, and after washing their hair. The scalp shows a diffuse reduction in hair density. The causes are described below.

Male and female patterns (androgenetic alopecia)

Male pattern baldness is inherited (the exact mode is unclear) and androgen dependent. Over several cycles, the androgen-sensitive follicles miniaturize from terminal to vellus hairs. Males are affected from the second decade and, by the seventh decade, 80% have involvement. Pattern balding also occurs in females, the majority of whom are hormonally normal. It becomes more pronounced after menopause and is present in 70% of 80-year-old women. In men, bitemporal recession followed by a bald crown is the usual pattern (Fig. 35.1); women may show this but more commonly exhibit a diffuse thinning. Mostly, no treatment is required but, if indicated, topical minoxidil (Regaine) produces some response in one-third of cases, and finasteride can help. In men, hair transplantation is an option.

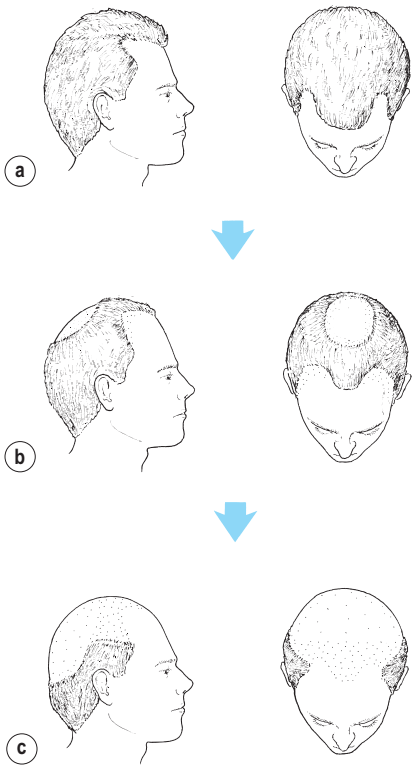


Fig. 35.1 Male pattern baldness. Hair loss may progress from bitemporal recession **(a)**, to vertex involvement **(b)**, to the most severe form **(c)**, where only a horseshoe of hair runs from the ears to the occiput.

Endocrine- and nutrition-related

Endocrine disorders often present with hair loss. Underactivity of the thyroid, pituitary or adrenals can cause diffuse alopecia, as may hyperthyroidism. Androgen-secreting tumours in women produce male pattern baldness with virilization. Malnutrition induces dry brittle hair that becomes pale or red in kwashiorkor (protein deficiency). Diffuse hair loss is also seen with iron or zinc deficiency.

Telogen effluvium

Hair follicles are not usually in phase but, if synchronized into the telogen-resting mode, they will be shed in unison about 3 months later. Such an *effluvium* can be a response to high fever, childbirth, surgery, drug reaction or other stress.

Drug-induced

Abrupt cessation of growth (*anagen effluvium*) may follow ingestion of a poison such as thallium, but is more commonly drug-induced, e.g. with cytotoxics (especially cyclophosphamide), heparin, warfarin, carbimazole, colchicine and vitamin A.

Localized non-scarring alopecia

Patchy hair loss results from a variety of causes, as described below.

Alopecia areata

Alopecia areata is a common condition, associated with autoimmune disorders, in which anagen is prematurely arrested. It generally starts in the second or third decade and presents with sharply defined non-inflamed bald patches on the scalp. Pathognomonic exclamation-mark (!) hairs, which taper as they approach the scalp, are seen. The eyebrows and beard can also be affected, and nails may show pitting.

The course is unpredictable: bald patches may enlarge progressively but, for a first attack, regrowth (often initially with white hairs) is usual (Fig. 35.2). Prepubertal onset, extensive involvement (especially of the posterior scalp) and atopy signal a poor prognosis. Complete scalp alopecia (totalis) or loss of all bodily hair (universalis) is seen occasionally. Rarely, diffuse scalp alopecia occurs.

Treatment depends on the extent: if localized, spontaneous regrowth is probable, and intralesional steroid (e.g. triamcinolone acetonide) may accelerate this. If extensive, therapy is less successful. Contact immunotherapy by the application of the sensitizer diphencyprone is effective but not widely available. Wigs are often necessary.

Infections

Scalp ringworm infection can result in patchy hair loss and is described below. Secondary syphilis causes a patchy alopecia.

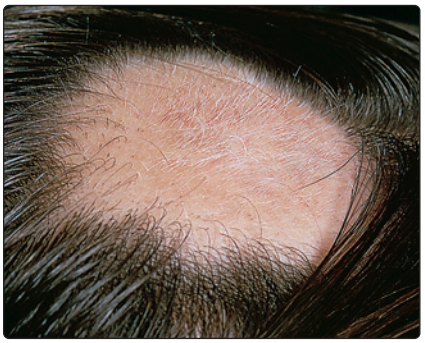


Fig. 35.2 Alopecia areata showing some exclamation mark (!) hairs and growth of white hair.

Psychological distress: Doctors treating patients with hair loss should appreciate the psychological distress that often accompanies the problem, especially in women (but affecting men as well). Scalp hair is an integral part of a person's self-image and 'face to the world', hence the considerable amount of money spent on hairdressing and hair cosmetics. Offering psychological support as well as active treatment should be part of the overall management plan. Patient help-groups can offer support to those who are distressed. Alopecia UK (http://www.alopeciaonline.org.uk/) and Alopecia Awareness (http://www.alopecia-awareness.org.uk/) can be helpful.

Hair transplantation can be used to treat male-pattern hair loss, usually in men. It needs to be done in carefully selected cases and by doctors who are experienced in the procedure, its indications and its potential complications. In hair transplantation, hair follicles are taken from an area of the skin not affected (and not likely to be affected) by androgenetic hair loss, e.g. the posterior hair line at the neck, and transplanted into the deficient area (often the frontal hairline).

The course is unpredictable: bald patches may enlarge progressively but, for a first attack, regrowth (often initially with white hairs) is usual (Fig. 35.2 and Fig. e35.1). Prepubertal onset, extensive involvement (especially of the posterior scalp) and atopy signal a poor prognosis. Complete scalp alopecia (totalis) or loss of all bodily hair (universalis) is seen occasionally. Rarely, diffuse scalp alopecia occurs.

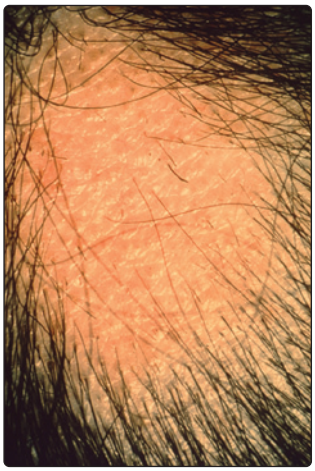


Fig. e35.1 Alopecia areata: a localized area of hair loss. Exclamation mark hairs (!) are evident on close inspection. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

Trauma and traction

Constantly rubbing or pulling the hair can result in its loss. Traction from tight rollers or pulling hair into a bun causes alopecia at the scalp margins. Hair straightening, bleaching and permanent waving produces a damaged hair shaft that is easily broken.

Localized/diffuse scarring alopecia

In scarring (cicatricial) alopecia, hair follicles are destroyed. This condition can result from the following:

- *Burns or irradiation*. Chemical or thermal burns will scar the scalp, as may X-irradiation, which was used in the past to induce epilation in the treatment of scalp ringworm.
- *Infection*. Shingles of the first trigeminal dermatome (p. 57), kerion (see below) and tertiary syphilis may leave a scarred scalp.
- *Lichen planus/lupus erythematosus*. Scarring alopecia of the scalp is seen, with erythema, scaling and follicular changes (Fig. 35.3). Lesions may exist elsewhere. Topical or intralesional steroids or systemic therapies are prescribed. Female frontal fibrosing alopecia may be a lichen planus variant.
- *Pseudopelade*. Pseudopelade describes a scarring alopecia, the end stage of an idiopathic or unidentified destructive inflammatory process in the scalp.

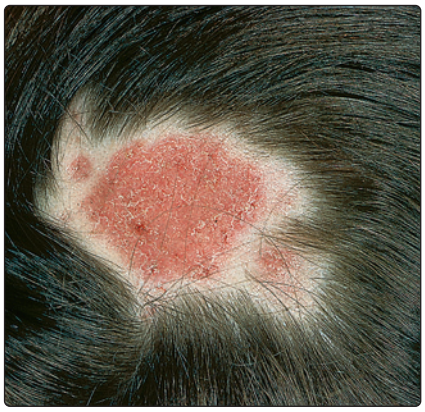


Fig. 35.3 Scarring alopecia due to discoid lupus erythematosus, which involves the scalp with erythema and scaling.

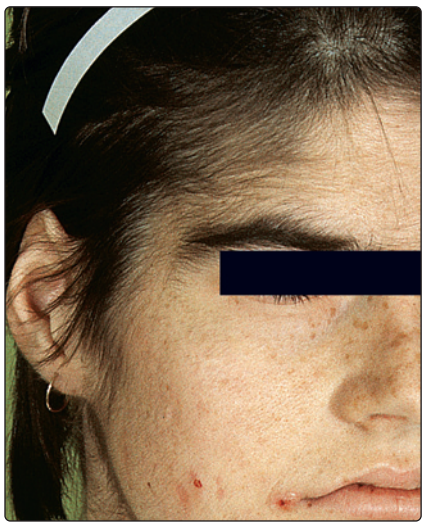


Fig. 35.4 Hypertrichosis in the face due to ingestion of minoxidil.

Excess hair (hirsutism and hypertrichosis)

Hirsutism is the growth of terminal hair in a male pattern in a female. It is quite common and presents with hair growth in the beard area, around the nipples and in the male pubic pattern. It frequently causes a lot of anxiety, even if mild. Hirsutism in many women is racial or idiopathic (Table 35.2) but some will have the polycystic ovary syndrome (PCOS), in which there may be associated acne, raised blood androgens, irregular periods and ovarian cysts on ultrasound. Few cases are due to an androgen-secreting tumour, although it is important to identify virilizing features such as cliteromegaly, male pattern baldness and a deep voice that might indicate this. In hirsutism, endocrine investigations are usually indicated. *Hypertrichosis* is less common and is defined as excessive terminal hair growth in a non-androgenic distribution, in which fine terminal hair appears on the face, limbs and trunk (Fig. 35.4). It is mostly drug-induced (Table 35.3).

Table 35.2 Causes of hirsutism

Type	Example
Pituitary	Acromegaly
Adrenal	Cushing syndrome, virilizing tumours, congenital adrenal hyperplasia
Ovarian	Polycystic ovaries, virilizing tumours
Iatrogenic	Androgens, progestogens
Idiopathic	End-organ hypersensitivity to androgens

Table 35.3 Causes of hypertrichosis

Type	Example
Localized	Melanocytic naevi, faun tail (associated with spina bifida occulta), chronic scarring or inflammation
Generalized	Malnutrition in children, anorexia nervosa, porphyria cutanea tarda, underlying malignancy, drugs, e.g. minoxidil, phenytoin, ciclosporin

Treatment of hirsutism is often unsatisfactory. Electrolysis is time consuming for large areas. Waxing, shaving and bleaching are other approaches. Laser hair removal is widely available. Treatment with an antiandrogen (cyproterone acetate), usually with ethinylestradiol, is occasionally effective. Eflornithine cream helps facial hair. PCOS can be treated with metformin and spironolactone. Hypertrichosis requires investigation to find the underlying cause.

Other disorders

Hair shaft defects are rare, usually inherited, conditions of the hair shaft (e.g. monilethrix) that result in broken hairs that are brittle, beaded and look abnormal.

Dandruff is an exaggerated physiological exfoliation of fine scales from an otherwise normal scalp. More severe forms merge with seborrhoeic dermatitis of the scalp (p. 62). Psoriasis (p. 30) produces scaling and may give localized alopecia.

Tinea capitis usually affects children. Common causative organisms and recommended treatments are shown on page 61. Anthropophilic species cause defined scaly areas with slight inflammation and alopecia with broken hair shafts. Zoophilic infection with *Trichophyton verrucosum* produces an inflamed boggy, pustular swelling known as a kerion (Fig. e35.4). Scarring may result. Infection with *T. schoenleinii* causes favus – a chronic crusted scarring alopecia.

Common hair disorders

- **Male pattern baldness:** the commonest cause of hair loss; if treatment is required, topical minoxidil or oral finasteride may help.
- **Alopecia areata:** common; discrete bald patches may show exclamation-mark (!) hairs. Early cases recover spontaneously.
- **Scarring alopecia:** needs investigation to establish the underlying cause.
- **Hirsutism:** may be due to polycystic ovary disease. Endocrine investigations are indicated. Androgen-secreting virilizing tumours are uncommon.

The treatment of the permanently scarred scalp can be difficult. Scalp surgery, for example the excision of an area of scarring alopecia and direct closure, or the use of a balloon expander to produce sufficient scalp skin to cover a defect, is occasionally appropriate.

Hirsutism is the growth of terminal hair in a male pattern in a female (Fig. e35.2). Hirsutism is usually a problem in women and, as with alopecia, can be psychologically damaging. It is quite common and presents with hair growth in the beard area, around the nipples and in the male pubic pattern. It frequently causes a lot of anxiety, even if mild. Hirsutism in many women is racial or idiopathic (Table 35.2) but some will have the polycystic ovary syndrome (PCOS), in which there may be associated acne, raised blood androgens, irregular periods and ovarian cysts on ultrasound. Few cases are due to an androgen-secreting tumour, although it is important to identify virilizing features such as cliteromegaly, male pattern baldness and a deep voice that might indicate this. In hirsutism, endocrine investigations are usually indicated. *Hypertrichosis* is less common and is defined as excessive terminal hair growth in a non-androgenic distribution, in which fine terminal hair appears on the face, limbs and trunk (Fig. 35.4 and Fig. e35.3). It is mostly drug-induced (Table 35.3).

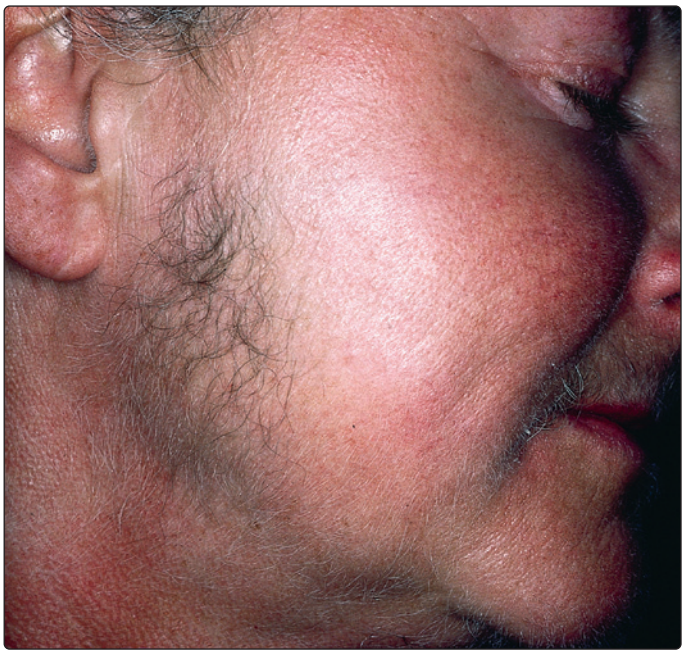


Fig. e35.2 A woman showing familial facial hirsutism. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Tinea capitis usually affects children (Fig. e35.4). Common causative organisms and recommended treatments are shown on page 60. Anthropophilic species cause defined scaly areas with slight inflammation and alopecia with broken hair shafts. Zoophilic infection with *Trichophyton verrucosum* produces an inflamed boggy, pustular swelling known as a kerion (Fig. e35.4). Scarring may result. Infection with *T. schoenleinii* causes favus – a chronic crusted scarring alopecia.

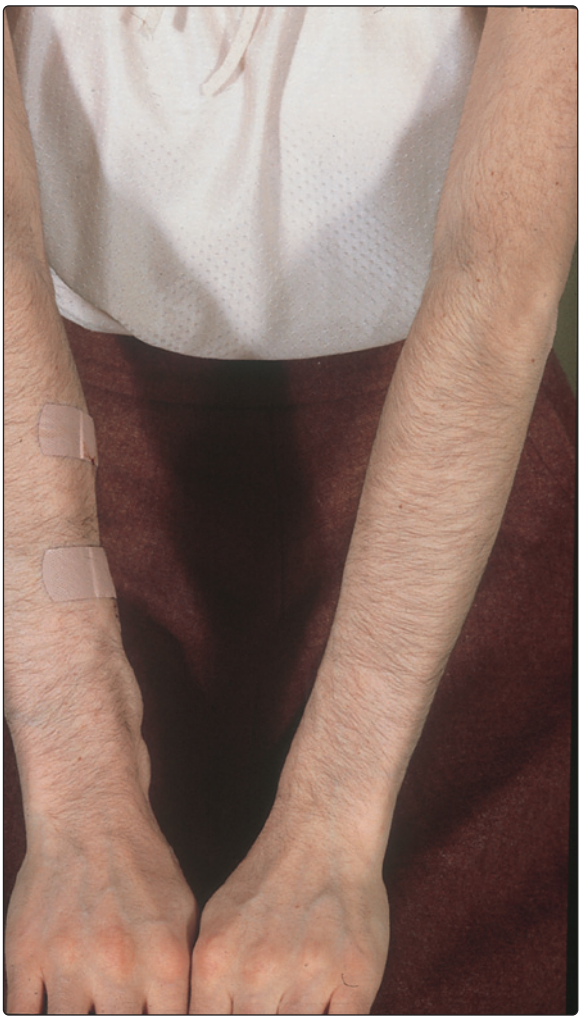


Fig. e35.3 Hypertrichosis on the arm due to ingestion of minoxidil. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

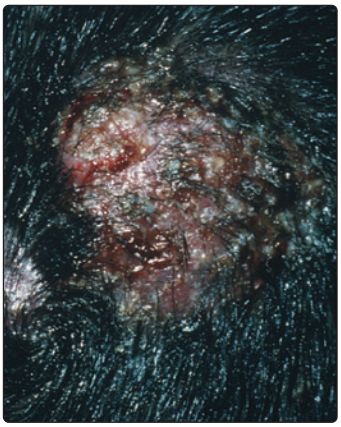


Fig. e35.4 Scalp ringworm (tinea capitis). Hair loss, crusting and scaling are present. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

Patient self-help organizations

Patient help groups can offer support to those who are distressed. They include Alopecia UK (http://www.alopeciaonline.org.uk/) and Alopecia Awareness (http://www.alopecia-awareness.org.uk/).

Further reading – online sources

Websites that can give further details on hair loss disorders and on problems of excessive hair are NHS Choices (http://www.nhs.uk/conditions/) and the Mayo Clinic (http://www.mayoclinic.org/diseases-conditions/).

Further reading – textbooks

Dawber, R., van Neste, D., 2007. Hair and Scalp Disorders, second ed. Martin Dunitz, London.
van Neste, D., Lachapelle, J.M., Antoine J.L., (eds) 2012. Trends in Human Hair Growth and Alopecia Research. Kluwer, Dordrecht.

36 Disorders of nails

Congenital disease

A number of usually rare congenital conditions can affect the nails. In *nail–patella syndrome*, the nails (and patellae) are absent or rudimentary. The nails in *pachyonychia congenita* are thickened and discoloured from birth. *Racket nails*, characterized by a broad short thumbnail, is the commonest congenital nail defect. It is dominantly inherited and more common in women. Nail dystrophy is a feature of *dystrophic epidermolysis bullosa* (p. 95).

Trauma

Trauma, especially from sport, commonly causes nail abnormalities. *Subungual haematomas* usually occur when a fingernail has been trapped or a toenail stood on or stubbed, but the possibility of a subungual malignant melanoma must always be considered. *Splinter haemorrhages* are induced by trauma, although they also occur with infective endocarditis. Ill-fitting shoes contribute to *ingrowing toenails*, and chronic trauma predisposes to *onychogryphosis* – in which the big toenails become thickened and grow like a horn. Trauma may also induce onycholysis (separation of the nail from the nail bed). Constant picking of the thumbnail will produce *a habit-tic dystrophy* with transverse ridges and grooves. *Brittle nails* are a common complaint, usually due to repeated exposure to detergents and water, although iron deficiency, hypothyroidism and digital ischaemia are other causes.

Dermatoses

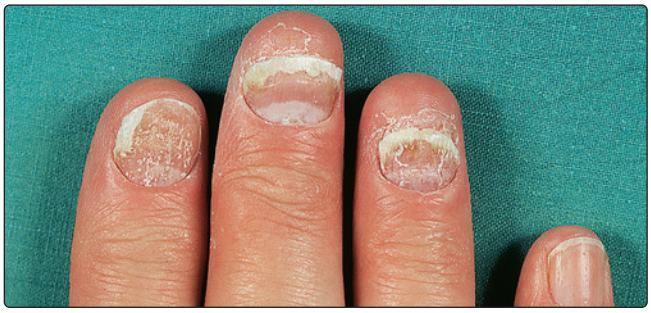


Fig. 36.1 Psoriasis of the nails. Pitting, onycholysis and brownish discoloration are apparent.

Table 36.1 **Nail involvement in common dermatoses**

Dermatosis	Nail changes
Alopecia areata	Fine pitting, roughness of nail surface
Darier's disease	Longitudinal ridges, triangular nicks at distal nail edge
Eczema	Coarse pitting, transverse ridging, dystrophy, shiny nails due to rubbing
Lichen planus	Thinned nail plate, longitudinal grooves, adhesion between distal nail fold and nail bed (pterygium), complete nail loss
Psoriasis	Pitting, nail thickening, onycholysis (separation of nail from nail bed), brown discoloration, subungual hyperkeratosis

The nails are commonly involved in skin disease (Figs 36.1, 36.2), and are routinely assessed in a dermatological examination. Details are given in Table 36.1, and a differential diagnosis of the changes is shown in Table 36.2. Treatment is aimed at the associated dermatosis; care of the hands (p. 37) is especially important.

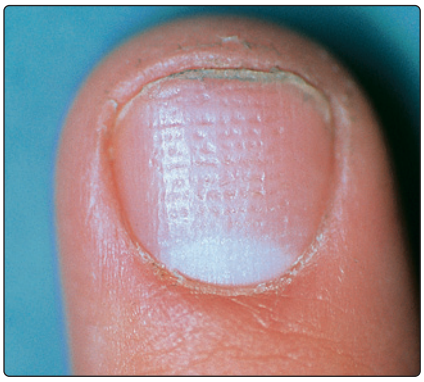


Fig. 36.2 Alopecia areata. Thimble pitting of the nail is seen.

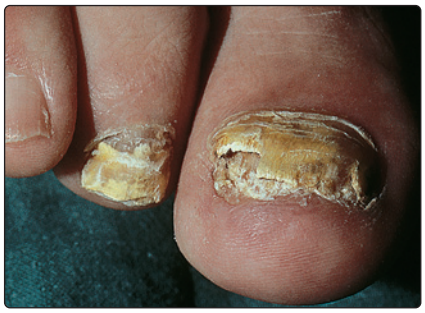


Fig. 36.3 Fungal infection of toenails. The nails are thickened, crumbly and discoloured. An adjacent nail is not affected. Dermatophytes, *C. albicans* and, occasionally, moulds such as *Fusarium* or *Scopulariopsis brevicaulis* are causative.

Infections

Bacterial or fungal infection may involve the nail fold (paronychia) or the nail itself.

Onychomycosis (tinea unguium)

Fungal infection of the nails (onychomycosis) increases with age; children are seldom affected. Toenails, especially the big toenails (Fig. 36.3), are involved more than fingernails. The process usually begins at the distal nail edge and extends proximally to involve the whole nail. The nail separates from the nail bed (onycholysis), the nail plate becomes thickened, crumbly and yellow, and subungual hyperkeratosis occurs. Several – but almost never all – of the toenails may be involved. Tinea pedis often coexists and, if the fingernails are diseased, *Trichophyton rubrum* infection of the hand is usually seen. Treatment is with oral terbinafine (Lamisil) or itraconazole (Sporanox).

Chronic paronychia

Chronic paronychia of the fingernails due to *Candida albicans* is often seen in wet workers. The cuticle is lost, the proximal nail fold becomes boggy and swollen (Fig. 36.4) and light pressure may extrude pus. The nail plate becomes irregular and discoloured. Gram-negative bacteria may be co-pathogens and turn the nail a blue–green colour. Management is directed towards keeping the hands dry, applying an imidazole lotion or cream to the nail fold twice daily, or oral itraconazole for 14 days.

Acute paronychia

Acute paronychia is usually bacterial, and staphylococci are often the cause. Oral flucloxacillin or erythromycin is required.

Trachyonychia describes a dystrophic process characterized by roughness, thinning of the nail plate and excessive longitudinal ridging involving all 20 nails ('20 nail dystrophy', Fig. e36.1). It is associated with alopecia areata, lichen planus, psoriasis and eczema.

Fungal infection of the nails (onychomycosis) increases with age; children are seldom affected. Toenails, especially the big toenails (Fig. 36.3), are involved more than fingernails. The process usually begins at the distal nail edge and extends proximally to involve the whole nail (Fig. e36.2). The nail separates from the nail bed (onycholysis), the nail plate becomes thickened, crumbly and yellow, and subungual hyperkeratosis occurs. Several – but almost never all – of the toenails may be involved. Tinea pedis often coexists and, if the fingernails are diseased, *Trichophyton rubrum* infection of the hand is usually seen. Treatment is with oral terbinafine (Lamisil) or itraconazole (Sporanox).

Fig. e36.1 Trachyonychia. Roughness, thinning of the nail plate and excessive longitudinal ridging are seen. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

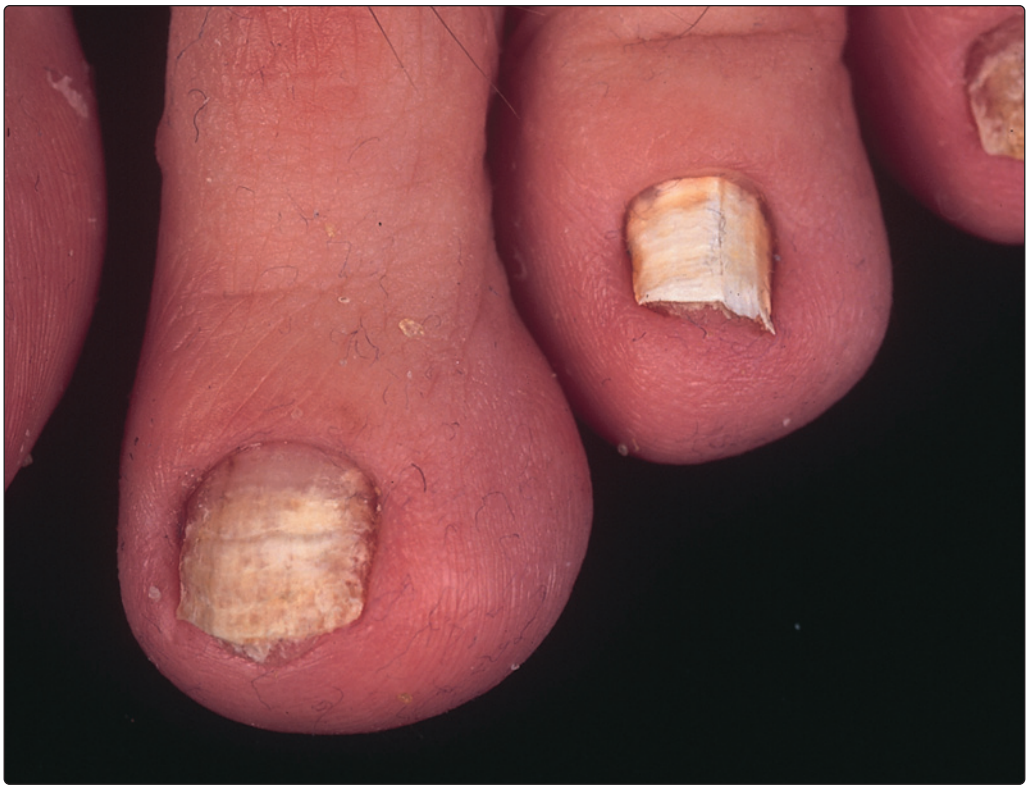


Fig. e36.2 Fungal infection of a toenail involving the entire length of the nail. This is a variant called white superficial onychomycosis. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

Table 36.2 **Differential diagnosis of nail changes in dermatoses and systemic disease**

Change	Description of nail	Differential diagnosis
Beau's lines	Transverse grooves	Any severe systemic illness that affects growth of the nail matrix
Brittle nails	Nails break easily, usually at distal margin	Effect of water and detergent, iron deficiency, hypothyroidism, digital ischaemia
Colour change	Black transverse bands	Cytotoxic drugs
	Blue	Cyanosis, antimalarials, haematoma
	Blue–green	*Pseudomonas* infection
	Brown	Fungal infection, stain from cigarette smoke, chlorpromazine, gold, Addison's disease
	Brown 'oil stain' patches	Psoriasis
	Brown longitudinal streak	Melanocytic naevus, malignant melanoma, Addison's disease, racial variant
	Red ('splinter haemorrhages')	Infective endocarditis, trauma
	White spots	Trauma to nail matrix (not calcium deficiency)
	White transverse bands	Heavy metal poisoning
	White/brown 'half and half' nails	Chronic renal failure
	White (leuconychia)	Hypoalbuminaemia (e.g. associated with cirrhosis)
	Yellow	Psoriasis, fungal infection, jaundice, tetracycline
	Yellow nail syndrome (Fig. 36.5)	Defective lymphatic drainage – pleural effusions may occur
Clubbing	Loss of angle between nail fold and nail plate, bulbous fingertip, nail matrix feels spongy	*Respiratory*: bronchial carcinoma, chronic infection, fibrosing alveolitis, asbestosis *Cardiac*: infective endocarditis, congenital cyanotic defects *Other*: inflammatory bowel disease, thyrotoxicosis, biliary cirrhosis, congenital
Koilonychia	Spoon-shaped depression of nail plate	Iron deficiency anaemia; also lichen planus and repeated exposure to detergents
Nail fold telangiectasia	Dilated capillaries and erythema at nail fold	Connective tissue disorders including systemic sclerosis, systemic lupus erythematosus, dermatomyositis
Onycholysis	Separation of nail from nail bed	Psoriasis, fungal infection, trauma, thyrotoxicosis, tetracyclines (*photo-onycholysis*)
Pitting	Fine or coarse pits may be seen in nail bed	Psoriasis, eczema, alopecia areata, lichen planus
Ridging	Transverse (across nail) Longitudinal (up/down)	Beau's lines (see above), eczema, psoriasis, tic-dystrophy, chronic paronychia, lichen planus, Darier's disease

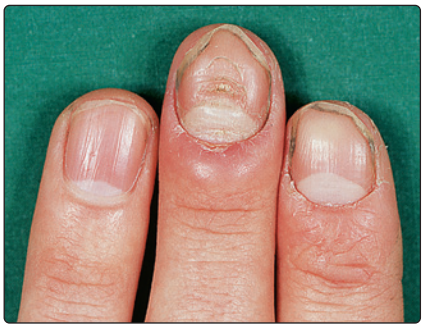


Fig. 36.4 *C. albicans* is the commonest pathogen in chronic paronychia. The nail fold is inflamed and swollen, and the nail is ridged transversely.

Systemic disease

Nail changes not infrequently indicate an underlying internal medical disorder. Table 36.2 shows some systemic associations.

Fig. 36.5 Yellow nail syndrome. The nails grow very slowly, lymphatic drainage is abnormal, and pleural effusions may occur.

Tumours

Cancers of the nail and nail bed are rare, but it is not uncommon to see benign tumours around the nail fold. Examples of both include the following:

- *Viral warts*. Periungual warts are common. Treatment is similar to that for warts elsewhere (p. 54.e1).
- *Periungual fibromas*. These are seen in patients with tuberous sclerosis (p. 96) and appear at or after puberty.
- *Myxoid (mucous) cysts*. The cysts appear adjacent to the proximal nail fold, usually on the fingers. They are fluctuant, semi-translucent papules that contain a clear gel and may arise from folds of synovium. Treatment is by cryotherapy, injection with triamcinolone acetonide (a steroid) or excision.
- *Malignant melanoma*. A subungual malignant melanoma should be excluded by biopsy if a pigmented longitudinal streak appears and progresses in a nail. An acral malignant melanoma may be amelanotic and can resemble a pyogenic granuloma or even chronic paronychia. Any atypical or ulcerating lesion around the nail fold requires a biopsy to exclude a malignant melanoma.

Disorders of nails

- **Congenital nail problems** are uncommon except for racket nails.
- **Sports trauma** often results in subungual haematoma, onychogryphosis or onycholysis.
- **Common dermatoses**, e.g. psoriasis, lichen planus and eczema have distinctive nail changes.
- **Fungal infection** of the big toenails is common, especially in the elderly. Oral terbinafine or itraconazole is prescribed if needed.
- **Chronic paronychia** of fingernails is due to *C. albicans*. Improved skin care, topical imidazole or oral itraconazole are suggested.
- **Acute paronychia** is usually bacterial: antibiotics are given.
- **Systemic diseases** may cause nail changes that help in diagnosis. Examples are clubbing, koilonychia or splinter haemorrhages.
- **Malignant melanoma** of the nail bed must be considered with any subungual pigmentation or nail destruction.

Further reading – online sources

There are several websites which give further information about nail diseases, including NHS Choices (access via http://www.nhs.uk/conditions/), Medline Plus (access via http://www.nlm.nih.gov/medlineplus/) and Hooked on Nails (access via http://www.hooked-on-nails.com/naildisorders.html).

Further reading – textbooks

Baran, R., de Berker, D., Holzberg, M., Thomas, L., 2012. Baran and Dawber's Diseases of the Nails and Their Management, fourth ed. Wiley-Blackwell, Oxford.

37 Vascular and lymphatic diseases

Blood vessel disorders

Erythema

Erythema is redness of the skin, usually due to vasodilatation (Table 37.1). It may be localized, e.g. with pregnancy or liver disease (on palms), fixed drug eruption and infection (e.g. Lyme disease), or generalized, as with drug eruption, toxic erythema (e.g. viral exanthem) and connective tissue disease.

Flushing

Flushing is erythema due to vasodilatation. The causes are:

- physiological (autonomic response to emotion, heat or exercise)
- menopausal (hormonal; often with associated sweating)
- foods (e.g. spices – gustatory; alcohol – aldehyde-related)
- drugs (angiotensin-converting enzyme [ACE] inhibitors, 5-hydroxytryptamine [5-HT_3] antagonists, nifedipine)
- rosacea (mechanism unknown)
- carcinoid syndrome (serotonin – 5-HT)
- phaeochromocytoma (catecholamine).

Flushing is common and affects the face, neck and upper trunk. It is usually benign. A sudden onset and systemic symptoms (e.g. diarrhoea or fainting) mean that carcinoid syndrome or phaeochromocytoma must be excluded. In treatment, first remove the cause, e.g. spices or alcohol. Embarrassing physiological flushing may improve with a small dose of propranolol.

Telangiectasia

Telangiectasia is a visible dilatation of dermal venules or, in spider naevi (Fig. 37.1), an arteriole. It results from:

- *congenital* (e.g. hereditary haemorrhagic telangiectasia)
- *skin atrophy* (topical steroids, ageing skin, radiation dermatitis)
- *excess oestrogen* (e.g. liver disease, pregnancy, 'the pill')
- *connective tissue disease* (systemic sclerosis, lupus erythematosus, dermatomyositis)
- *rosacea* (on the face)
- *venous disease* (lower leg).

Isolated spider naevi are common and of little significance, but their number may increase with pregnancy and liver disease. A venous lake – an acquired form of venous ectasia – is often seen on the lower lip of the elderly. Telangiectasia is treated by fine-needle cautery, hyfrecation or laser (p. 115).

Table 37.1 **Classification of blood vessel and lymphatic disorders**

Vessel	Process	Resulting lesion
Small blood vessels	Dilatation (and/or increased flow)	Erythema, flushing, telangiectasia
	Release of extracellular fluid	Urticaria (p. 80), oedema
	Release of blood	Purpura, capillaritis
	Reduced flow	Livedo reticularis, chilblains, Raynaud's phenomenon
	Inflammation damage	Vasculitis, erythema ab igne
Arteries	Atherosclerosis, Buerger's disease	Ischaemia and ulceration
	Inflammation	Vasculitis (p. 86)
Veins	Inflammation, flow reduction, clotting abnormalities	Thrombosis, skin changes, ulceration (p. 76)
	Dilatation	Venous lake
Lymphatics	Congenital hypoplasia	Lymphoedema (primary)
	Blockage or inflammation	Lymphoedema (secondary)
	Infection	Lymphangitis

Purpura

Purpura is a blue–brown discoloration of the skin due to the extravasation of erythrocytes (Fig. 37.2). It results from a variety of mechanisms:

- Vessel wall defects:
  - vasculitis (e.g. due to immune complexes), paraproteinaemia (e.g. cryoglobulinaemia)
  - infection (e.g. meningococcaemia)
  - raised vascular pressure (e.g. venous disease).
- Defective dermal support:
  - dermal atrophy (ageing, steroids, disease, e.g. lichen sclerosus)
  - scurvy (vitamin C deficiency).
- Clotting defects:
  - coagulation factor deficiency (e.g. disseminated intravascular coagulation) or inherited
  - anticoagulant (heparin, warfarin)
  - thrombocytopenia of any cause
  - abnormal platelet function.
- Idiopathic pigmented purpuras.

Petechiae are small dot-like purpura, whereas ecchymoses are more extensive. Purpura is often seen in the elderly or those on steroids, and develops spontaneously or after minor trauma. Idiopathic pigmented purpura is seen as brownish punctate lesions (capillaritis) on the legs.

Mostly, there is no specific therapy. Underlying causes, e.g. blood disorders or vasculitis, are treated as necessary.

Raynaud's phenomenon

Raynaud's phenomenon is characterized by a paroxysmal vasoconstriction of the digital arteries, usually provoked by cold, in which the fingers turn white (due to ischaemia), cyanotic blue (due to capillary dilatation with a stagnant blood flow) and then red (due to reactive hyperaemia). When no cause is found, it is known as 'Raynaud's disease'. Causes include:

- *arterial occlusion*: atherosclerosis, Buerger's disease
- *connective tissue disease*: systemic sclerosis (including CREST syndrome, p. 84), systemic lupus erythematosus (p. 84)
- *hyperviscosity syndrome*: polycythaemia, cryoglobulinaemia
- *neurological defects*: syringomyelia, peripheral neuropathy

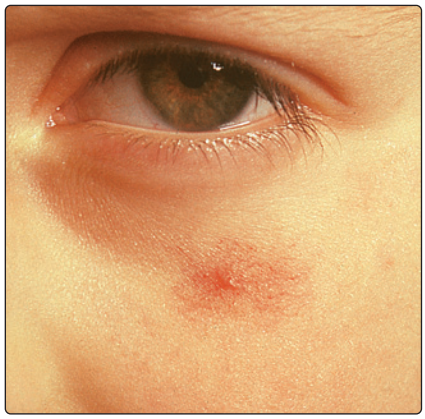


Fig. 37.1 A spider naevus on the cheek of a child.

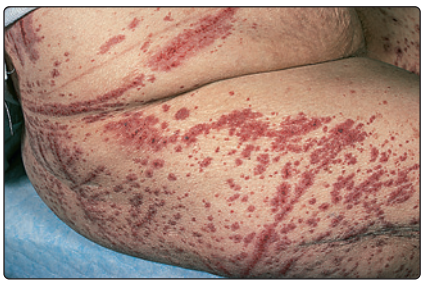


Fig. 37.2 Purpura in a patient with thrombocytopenia.

Schaumberg's disease (progressive pigmented purpura) is the commonest type of idiopathic capillaritis (Fig. e37.1a). It typically presents as crops of reddish-brown colour change with cayenne-pepper petechiae, most frequently located to the lower legs. No cause is known. The course is often protracted with recurrent crops. There are no symptoms.

Raynaud's phenomenon is characterized by a paroxysmal vasoconstriction of the digital arteries, usually provoked by cold, in which the fingers turn white (due to ischaemia), cyanotic blue (due to capillary dilatation with a stagnant blood flow) and then red (due to reactive hyperaemia) (Fig e37.1b). When no cause is found, it is known as 'Raynaud's disease'. Causes include:

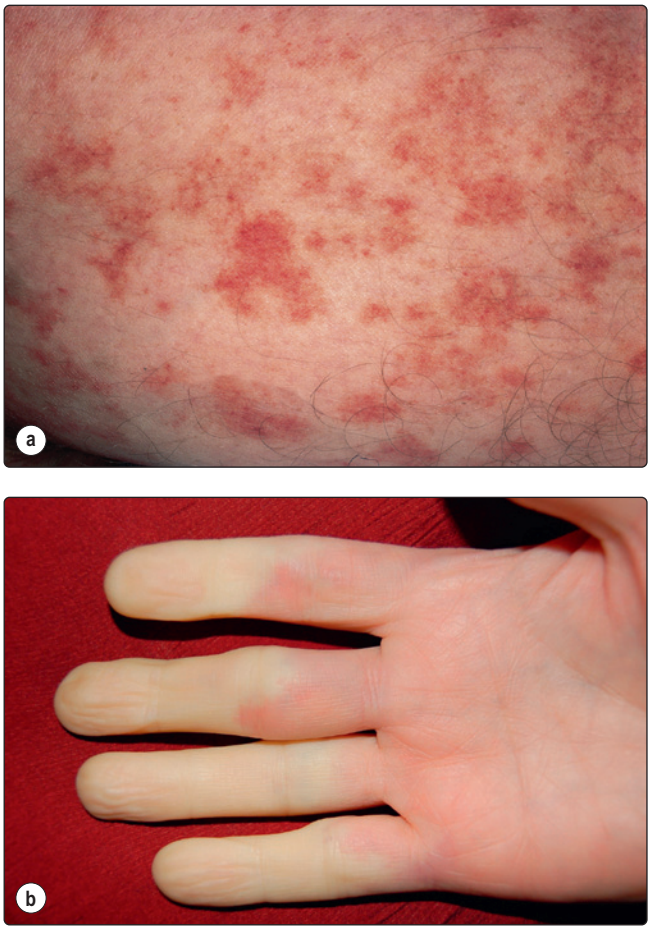


Fig. e37.1 (a) Schamberg's progressive pigmented purpura. Reddish-brown patches with a yellow tinge are superimposed on petechiae. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)* **(b) Raynaud's phenomenon.**

- *reflux vasoconstriction*: with use of vibration tools (p. 133.e1)
- *toxins/drugs*: ergot, vinyl chloride, beta-blockers.

Raynaud's phenomenon mostly affects women. It may be the forerunner of a connective tissue disease. The hands should be kept warm and protected from the cold. Smoking must be stopped. A calcium channel blocker (e.g. nifedipine) or naftidrofuryl may help. In resistant cases, epoprostenol (prostacyclin) infusions are given.

Livedo reticularis

Livedo reticularis is a marble-patterned cyanosis of the skin, due to reduced arteriole blood flow, usually in women. The condition has the following causes:

- *Physiological*, i.e. cold induced.
- *Vasculitis* due to connective tissue disease, e.g. systemic lupus erythematosus and polyarteritis nodosa.
- *Hyperviscosity* due to cryoglobulinaemia, polycythaemia.
- *Sneddon syndrome*, which consists of livedo vasculitis with cerebrovascular disease and circulating antiphospholipid antibodies.

Cold-induced livedo reticularis gives a mottled meshwork pattern on the outer thighs of children and is reversible. Fixed livedo (Fig. 37.3) is due to vasculitis and requires investigation. Treatment is aimed at the underlying disease.

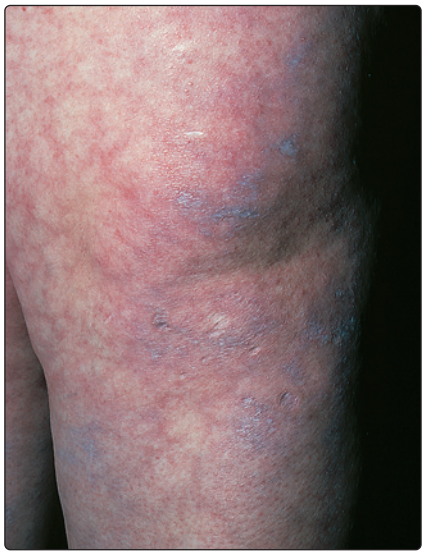


Fig. 37.3 Livedo reticularis. In this case, the condition was associated with systemic lupus erythematosus.

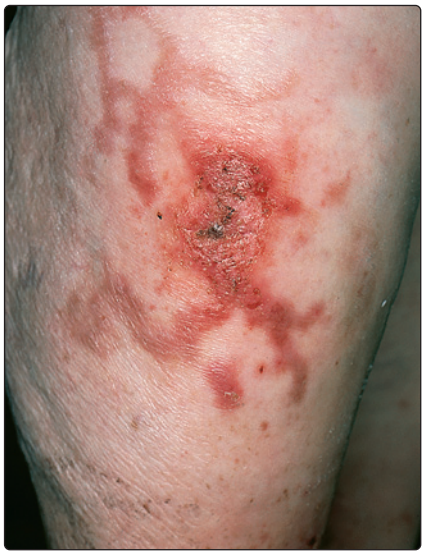


Fig. 37.4 Erythema ab igne on the upper outer shin from sitting in front of a fire.

Erythema ab igne

Erythema ab igne is a reticulate pigmented erythema (Fig. 37.4) due to heat-induced damage. It is seen on the shins of the elderly who sit before a fire, or with the use of heat pads or laptop computers.

Chilblains

Chilblains are inflamed and painful purple–pink swellings on the fingers, toes or ears that appear in response to cold. Chilblains result from an overcompensatory cold-induced vasoconstriction of cutaneous arterioles and venules. They occur in the winter and usually affect women. Warm housing and clothing are advised. Oral nifedipine may help.

Lymphatic disorders

Lymphoedema

Lymphoedema is oedema, often of a limb, due to inadequate lymphatic drainage. The condition may be primary or secondary. Primary lymphoedema is the result of a congenital developmental defect. Secondary causes include:

- recurrent infection – lymphangitis
- blockage – filariasis, tumour
- destruction – surgery, radiation.

Primary lymphoedema presents in adolescence and may follow infection. The lower legs are commonly affected. In chronic lymphoedema, the oedema is non-pitting and fibrotic, and the overlying epidermis hyperkeratotic (Fig. 37.5). Radiolabelled lymphoscintigraphy (or magnetic resonance imaging [MRI] lymphangiography) shows the defect.

A lymphoedematous limb is at risk of repeated infection (particularly erysipelas), and long-term prophylaxis with oral phenoxymethylpenicillin is recommended. Exercise, compression support and massage can help. Surgical reconstruction is rarely possible.

Lymphangitis

Lymphangitis is defined as infection of the lymphatic vessels, usually due to streptococci. It presents as a tender red line extending proximally up a limb, usually from a focus of infection. Hospital admission is usually necessary. Therapy is with a suitable intravenous antibiotic (e.g. benzylpenicillin).

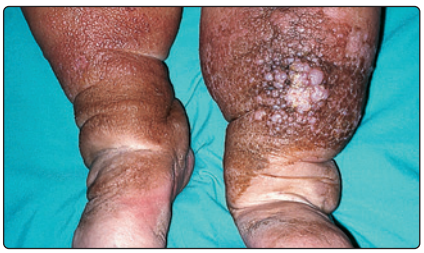


Fig. 37.5 Chronic lymphoedema of the legs with papillomatosis.

Vascular and lymphatic diseases

- **Erythema:** can be localized, e.g. liver palms, or generalized, e.g. toxic erythema.
- **Flushing:** usually emotional; rarely carcinoid syndrome or phaeochromocytoma.
- **Telangiectasia:** commonly seen with skin atrophy, but lesions can occur with oestrogen excess or connective tissue disease. Treatment is by hyfrecation or laser.
- **Purpura:** caused by defects of the vessel wall, supporting dermis or clotting mechanism, or 'idiopathic'. Treat the underlying disorder.
- **Livedo reticularis:** physiological or due to underlying hyperviscosity or connective tissue disorder. Investigation for systemic disease is usually indicated.
- **Chilblains:** describes cold-induced perniosis of the fingers, toes and ears.
- **Raynaud's phenomenon:** vasoconstriction of the digital arteries with colour changes.
- **Lymphoedema:** results from absence of or damage to lymphatics. Long-term prophylaxis with antibiotics prevents recurrent infection in chronic cases.

Patient self-help organizations

The Raynaud's and Scleroderma Association (http://www.raynauds.org.uk/) and the Scleroderma Society (http://sclerodermauk.org/) provide a useful contact point for patients suffering from these conditions. The Lymphoedema Support Network (http://www.lymphoedema.org/) provides help to patients with lymphoedema problems.

Further reading – online sources

Useful information about vascular disorders, Raynaud's disease and lymphoedema can be found at NHS Choices (access via http://www.nhs.uk/conditions/) and Medline Plus (access via http://www.nlm.nih.gov/medlineplus/). E-Learning for Healthcare (access via http://www.e-lfh.org.uk/programmes/dermatology/) is a potentially useful resource for dermatology trainees.

Further reading – textbooks

Mattassi, R., Loose, D.A., Vaghi, M. (Eds.), 2015. Hemangiomas and Vascular Malformations: An Atlas of Diagnosis and Treatment. Springer, Milano.

38 Leg ulcers

Leg ulcers affect 1% of the adult population and account for 1% of dermatology referrals. They are twice as common in women as in men and are a major burden on the health service. One-half is venous, one-tenth arterial and a quarter 'mixed' – due to venous *and* arterial disease. The remainder are due to rare causes.

Venous disease

Damage to the venous system of the leg results in pigment change, eczema, oedema, fibrosis and ulceration.

Aetiopathogenesis

The superficial low-pressure venous system of the leg is connected to the deep higher pressure veins by perforating veins. Blood flow relies on the pumping action of surrounding muscles and the integrity of valves. Valve incompetence, occasionally congenital but usually due to damage by thrombosis or infection, results in a rise in capillary hydrostatic pressure and permeability (Fig. 38.1). Fibrin is deposited as a pericapillary cuff, interfering with diffusion of nutrients and resulting in disease.

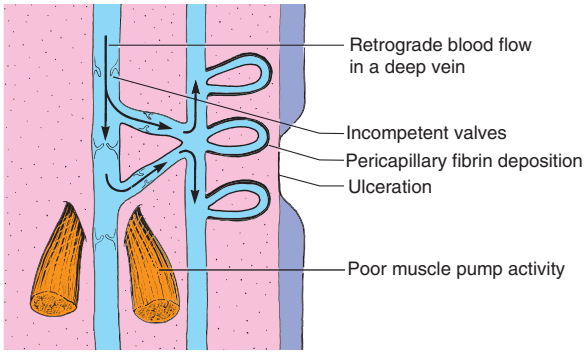


Fig. 38.1 The aetiopathogenesis of venous ulceration.

Clinical presentation

Venous disease usually starts in middle age and continues into later life. It is commoner in women and is predisposed to by obesity and venous thrombosis. Varicose veins are often present, but are not essential. The syndrome progresses through stages:

- *Heaviness and oedema*: early symptoms. The legs feel heavy and swell.
- *Discoloration*: brown haemosiderin deposits from extravasated red cells. Telangiectasia and white lacy scars (atrophie blanche) occur at the ankle (Fig. 38.2).
- *Eczema*: commonly occurs (p. 41), often complicated by allergic or irritant contact dermatitis.
- *Lipodermatosclerosis*: fibrosis of the dermis and subcutis around the ankle results in firm induration.
- *Ulceration*: often follows minor trauma, and typically affects the medial and, to a lesser extent, the lateral malleolus (Fig. 38.3). Neglected ulcers enlarge and may encircle the lower leg. Initially, venous ulcers are exudative but, under favourable conditions, they granulate and enter a healing phase in which the epidermis grows in from the sides and from small epithelial islands in the middle. Healing is invariably slow, often taking months. Some large ulcers never heal.

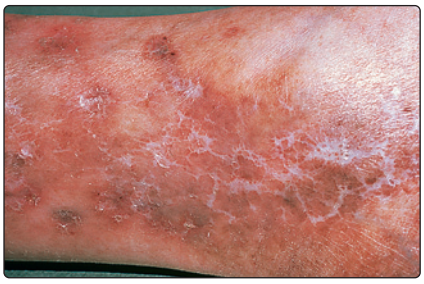


Fig. 38.2 Atrophie blanche with white lace-like scarring and haemosiderin deposition.

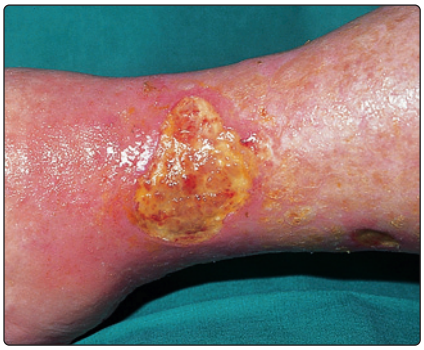


Fig. 38.3 A venous ulcer at the lateral malleolus.

- *Post-ulcer leg*: fibrosis may lead to a slender sclerosed ankle.

Differential diagnosis and complications

Venous ulcers can be differentiated from other ulcers (Table 38.1) by history, position and additional signs. Arterial ulcers are deep, painful and gangrenous, and situated on the foot or mid-shin. Complications of venous ulcers are common and include the following:

- *Infections*. Bacteria invariably colonize ulcers. Systemic antibiotics are needed only for overt infection, as suggested by a purulent discharge, a rapidly advancing ulcer edge, cellulitis or septicaemia.
- *Lymphoedema*. Lymphatic drainage is impaired in legs with chronic venous ulcers, adding to the oedema.

Table 38.1 Causes of leg ulceration

Division	Condition
Venous disease	Damaged valves (e.g. deep vein thrombosis), clotting disorder, congenital valve incompetence
Arterial disease	Atherosclerosis, Buerger's disease, polyarteritis nodosa
Small vessel disease	Diabetes mellitus, rheumatoid arthritis, vasculitis, sickle cell disease, hypertension
Infection	Tuberculosis, Buruli ulcer (p. 53), mycetoma (p. 65), syphilis (p. 126)
Neuropathy	Diabetes mellitus, leprosy, syphilis, syringomyelia
Neoplasia	Squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma
Trauma	Direct injury, artefact
Unknown	Pyoderma gangrenosum (p. 93), necrobiosis lipoidica (p. 88), hydroxycarbamide

- *Contact dermatitis*. Contact sensitivity to topical medicaments and bandages frequently develops, especially to lanolin, neomycin, rubber chemicals, fragrances and preservatives. Allergic contact dermatitis can resemble an exacerbation of venous eczema and is suspected if there is generalized secondary spread. Some local therapies, and the ulcer exudate itself, are irritant.
- *Malignant change*. Rarely, squamous cell carcinoma develops in an ulcer.

Management

Treatment of a leg ulcer is long term and progress is usually slow. The initial examination includes palpation of peripheral pulses and an assessment of contributing factors such as obesity, anaemia, cardiac failure and arthritis. Exclusion of coexisting arterial disease through the measurement of the ankle/brachial pressure index (ABPI) is mandatory when compression bandaging is proposed (p. 21). Treatments are as follows:

Venous ulcers are relatively easy to diagnose but difficult to treat, despite there being a lot of guidance available (search under leg ulcers, access via http://www.nhs.uk/).

Table 38.2 **Topical therapy for venous ulcers**

Type of wound	Role of dressing	Examples of dressing	Qualities of dressing
Dry, necrotic, black, yellow, sloughy	Moisture retention or rehydration, especially if dry; if moist, fluid absorption; removal of excess slough; possibly absorption of odour; possibly antimicrobial activity; infrequent changes so as not to disturb wound	Irrigation fluid, e.g. physiological saline	Use of irritant cleansers may be harmful; debris and dressing remnants can be removed with saline irrigation.
		Hydrocolloid, e.g. Comfeel Plus, Granuflex, DuoDERM Extra Thin or Aquacel	Hydrocolloid: absorbent layer on vapour-permeable film. Occlusive; facilitates rehydration/autolytic debridement of dry slough or necrotic wounds; promotes granulation; change daily or less frequently
		Larval therapy may be considered in suitable cases (see p. 77.e1)	
		Odour-absorbing dressing, e.g. Actisorb Silver 220, Lyofoam C	Absorbs odour; may bind bacteria; change daily or less frequently as dictated by clinical response
Clean, exudating, granulating	Fluid absorption; thermal insulation to give optimal temperature for healing; possibly odour absorption; possibly antimicrobial activity; optimal pH for wound healing	Alginate, e.g. Kaltostat, Sorbsan or SeaSorb	Highly absorbent; suitable for moderate/heavily exudating wounds; not for dry wound or eschar; change daily or less frequently
		Foam, e.g. Allevyn Thin or Lyofoam	Suitable for exudative wound; useful for overgranulation resulting from occlusive dressing; used as secondary dressing
		Low adherent tulle, e.g. Jelonet or Neotulle	Used as interface layer under a secondary absorbent dressing; medicated tulle dressings are not generally recommended
Dry, low exudate, epithelializing	Moisture retention or rehydration; low adherence; thermal insulation	Hydrogel, e.g. Aquaform, Intrasite Conformable	Amorphous cohesive material; takes shape of wound; needs secondary dressing; moisturizes/debrides dry wound

- *Compression bandages*. These reduce oedema and promote venous return. Bandages are applied from the toes to the knee. Self-adhesive bandages (e.g. Coban) are preferred, and are left on for 2–7 days. A four-layer bandage technique uses a layer of orthopaedic wool (e.g. Softexe), a standard crepe (e.g. Setocrepe), an elasticated bandage (e.g. Elset) and an elasticated cohesive bandage (e.g. Coban). Arterial disease precludes compression bandaging. Once an ulcer has healed, a toe-to-knee compression stocking maintains venous return.
- *Elevation, exercise and diet*. Some doctors recommend rest with leg elevation. Walking is encouraged, as is dieting for obese individuals and ankle exercises, to maintain joint mobility.
- *Topical therapy*. Table 38.2 shows what to use and when to use it. Venous eczema is treated with a mild to moderate potency steroid or an emollient.
- *Oral therapy*. Adequate analgesia is vital. Diuretics are given for cardiac oedema, and antibiotics for overt infection. An anabolic steroid, stanozolol (Stromba), may help lipodermatosclerosis, but side-effects (fluid retention, jaundice) limit its use. Oxerutins (Paroven) reduce capillary permeability, relieving oedema.
- *Surgery*. Vein surgery may prevent problems in younger patients, but is rarely applicable in the elderly. Split skin grafts or pinch grafts (from the thigh) are of limited use. Bilayer skin allografts can be helpful in venous ulcers that are slow to heal.

Arterial disease

Lower leg ischaemia and ulceration can result from arterial disease. Ischaemia

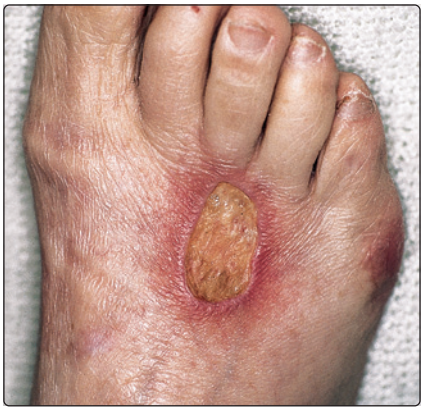


Fig. 38.4 An arterial ulcer on the dorsal aspect of the foot.

presents with claudication, coldness of the foot, loss of hair, toenail dystrophy and dusky cyanosis. Deep, sharply defined ulcers occur on the foot or mid-shin (Fig. 38.4). Pulses in the legs are absent or reduced. Buerger's disease, seen in young male smokers, is a severe form of arterial disease.

Doppler studies and magnetic resonance angiography define the arterial lesions, which may be amenable to vascular reconstruction or angioplasty. Compression bandaging is contraindicated if the ABPI is <0.5 but reduced compression may be used under supervision for ABPIs of 0.6–0.8.

Diabetic foot ulcers and other causes of leg ulceration

Foot ulcers are a common problem in people with diabetes and difficult to treat, requiring a multidisciplinary approach (Fig. 38.5). Risk factors include *neuropathy*, vascular disease and ill-fitting shoes. *Vasculitic ulcers* start as purpura, but become necrotic and punched out (see Table 38.1). *Buruli ulcer* and

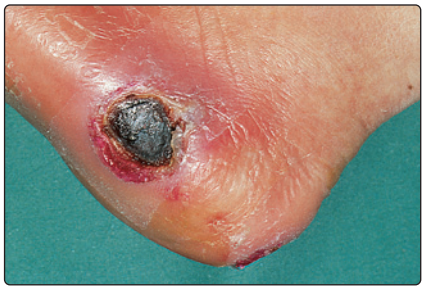


Fig. 38.5 A necrotic neuropathic ulcer on the side of the foot.

deep mycoses are important in the tropics. Hydroxycarbamide, used for haematological malignancies, is an occasional cause of leg ulcers.

Leg ulcers

Venous ulcers

- Result from venous hypertension.
- Show associated skin discoloration, eczema and fibrosis.
- Occur at the medial or lateral malleolus.
- Measuring the ABPI to exclude coexisting arterial disease is mandatory before compression bandaging.

Arterial ulcers

- Are associated with other symptoms and signs of leg ischaemia.
- Occur on the foot or mid-shin, are usually deep and painful.
- Prohibit most compression bandaging.

Diabetic foot ulcers

- Are common and difficult to treat, needing a multidisciplinary approach.
- Are due to a combination of neuropathy, vasculopathy, boney abnormalities and local pressure.

Other causes

- Vasculitis, trauma, neuropathy, hydroxycarbamide and some types of infection.

- *Occasional therapies*. Some treatments are used only occasionally. These include *larval therapy* with sterile maggots (available from BioMonde), which can be prescribed for sloughy leg ulcers. *Tissue-bioengineered skin bilayer equivalents*, e.g. Apligraf, can be effective in therapy-resistant wounds. There is recent evidence that orally administered simvastatin can improve healing time in venous ulcers (see Evangelista MT, Casintahan MF, Villafuerte LL. Simvastatin as a novel therapeutic agent for venous ulcers: a randomised double-blind placebo-controlled trial. Br J Dermatol 2014; 170: 1151–1157), though this observation requires confirmation.

Evidence-based approach to venous ulcer treatment

There have been many suggested treatments over the years, most of them topical therapies, that have fallen by the wayside once a dispassionate assessment has been undertaken. The Cochrane Team has made an evidence-based review of the available treatments and have devised an algorithm to guide therapy (access via http://www.woundsresearch.com/). In the review, they recommend:

- Debridement of the ulcer and exudate management
- Treatment of any systemic condition
- Multilayer compression bandaging; if this fails to achieve closure of <40% in 4 weeks, they suggest:
  - continue compression and wound management but add in bilayer skin allografts, up to five applications; if the ulcer heals they recommend:
    - compression stockings and appropriate skin care.

Diabetic foot ulcers

Foot ulcers affect 1 in 20 people with diabetes. Diabetic patients with foot ulcers often have reduced sensation from neuropathy, high pressures in the foot, callus formation, deformities such as prominent metatarsal heads and peripheral vascular disease.

Types of ulcer

Foot ulcers can be divided into the 'neuropathic', which affect the plantar aspects and the toes (associated with callus and high plantar pressures), and the 'neuroischaemic', which involve the edges of the foot such as the tips of the toes and the back of the heel (associated with ill-fitting footwear).

Prevention

The prevention of foot ulcers by attention to details of foot care is, not surprisingly, much preferred over trying to treat an ulcer once it has developed. A hydrating emollient, e.g. a non-greasy preparation such as Allpresan Diabetic Foot Foam Cream (containing urea as a humectant), may be beneficial in the care of the diabetic foot.

Treatment

Management is initially directed at debridement of necrotic tissue, wound dressings, relief of pressures on the foot and consideration of treating the vascular disease. Any indication of an infection in the foot should be treated as an emergency, requiring radiological assessment and microbiological culture of tissue samples (rather than would swabs). Any infection is treated with appropriate antibiotics and, if indicated, surgical intervention. *Recombinant platelet-derived growth factor* (becaplermin) is licenced for use in neuropathic ulcers, e.g. in diabetes.

Further reading – online sources

The NHS website and the Cochrane Organization provide further information (access via http://www.nhs.uk/ and http://www.woundsresearch.com/)

Further reading – textbooks

Grey, J., Harding, K. (Eds.), 2016. ABC of Wound Healing. BMJ Books, London.

39 Pigmentation

Skin colour is due to a mixture of the pigments melanin (p. 8), oxyhaemoglobin (in blood) and carotene (in the stratum corneum and subcutaneous fat). Pigmentary diseases are common and particularly distressing to those with darker skin. Disorders of pigmentation mainly involve melanocytes, but other causes are mentioned where relevant.

Hypopigmentation

Pigment loss may be generalized or patchy. Generalized hypopigmentation occurs with albinism, phenylketonuria and hypopituitarism; patchy loss is seen in vitiligo, after inflammation, following exposure to some chemicals and with certain infections (Table 39.1).

Vitiligo

Vitiligo is an acquired idiopathic disorder showing white non-scaly macules. The association with thyroid disease, pernicious anaemia and Addison's disease suggests an autoimmune aetiology in some cases. Thyroid function should be checked. About 30% of patients give a family history of the disorder. Melanocytes are absent from affected skin on histology.

Clinical presentation

Vitiligo affects 0.5% of the population, is seen in all races and is most troublesome in those with a dark skin. The sex incidence is equal, and the onset, usually between 10 and 30 years of age, may be precipitated by injury or sunburn. The sharply defined white macules are often symmetrical (Fig. 39.1). The hands, wrists, knees, neck and areas around orifices (e.g. the mouth) are frequently affected. Occasionally, vitiligo is segmental (e.g. down an arm), generalized or universal. The course is unpredictable; areas may remain static, spread or (infrequently) repigment. In light-skinned individuals, vitiligo may be discernible only in summer, when the non-vitiliginous areas become sun-tanned.

Differential diagnosis

Post-inflammatory hypopigmentation is often accompanied by other skin changes (Table 39.1). In chemical leucoderma, a history of exposure to phenolic chemicals should be sought. The hypopigmented macules of leprosy are normally anaesthetic.

Management

Treatment is unsatisfactory. Camouflage cosmetics require patience and skill to apply. Sunscreens help the lightly pigmented patient by reducing the tanning and contrast of the non-vitiligo areas. In patients with darker skin, topical potent steroids or tacrolimus can induce some repigmentation. Ultraviolet (UV) B or psoralen with UVA (PUVA) may help, although it can take months and any repigmentation might subsequently be lost. Rarely, depigmentation using *p*(Benzyloxy)phenol is considered when vitiligo is near universal, and other treatments have failed.

Albinism

Albinism is an autosomal recessive condition in which the melanocytes fail to synthesize pigment in the epidermis, hair bulb and eye.

Table 39.1 **Causes of hypopigmentation**

Cause	Example
Chemical	Substituted phenols, hydroquinone
Endocrine	Hypopituitarism
Genetic	Albinism, phenylketonuria, tuberous sclerosis, piebaldism
Infection	Leprosy, yaws, pityriasis versicolor
Post-inflammatory	Cryotherapy, eczema, psoriasis, morphoea, pityriasis alba
Other	Vitiligo, lichen sclerosus, halo naevus, scarring

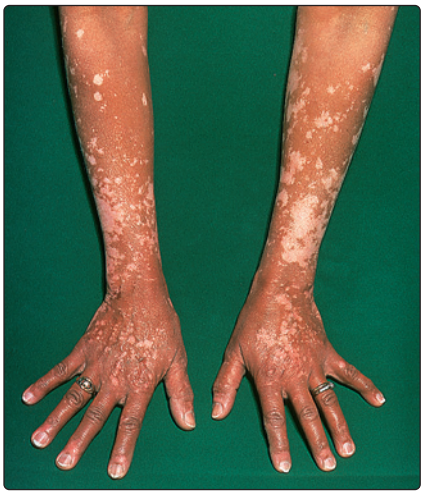


Fig. 39.1 Vitiligo showing symmetrical involvement of the forearms in a patient with pigmented skin.

There are several syndromes of albinism. All are autosomal recessive and show a lack of pigment in the skin, hair, iris and retina. Melanocyte numbers are normal, but melanosome production fails due to defective gene control of tyrosinase (p. 8).

Albinism is uncommon (the prevalence is 1/20,000), although the diagnosis is straightforward. The skin is white or pink, the hair white and pigmentation is lacking in the eye (Fig. 39.2). Albinos have poor sight, photophobia and nystagmus. 'Tyrosinase-positive' albinos may pigment slightly with age, so that black African skin becomes yellow and freckled. In the tropics, albinos risk premature skin photoageing and the early onset of skin tumours, especially squamous cell carcinomas.

Strict sun avoidance from childhood is essential. Opaque clothing, a wide-brimmed hat and sunscreens are needed. Prenatal diagnosis is possible.

Phenylketonuria

Phenylketonuria is an autosomal recessive inborn error of metabolism. Phenylalanine hydroxylase, which converts phenylalanine into tyrosine, is deficient. Phenylalanine and metabolites accumulate and damage the developing neonatal brain. The prevalence is 1/10,000 births.

Phenylketonuria is detected after birth by routine screening tests. Untreated, mental retardation and choreoathetosis develop. Patients have fair hair and skin, due to impaired melanin synthesis. Atopic eczema is common. A low phenylalanine diet, given early, prevents neurological damage.

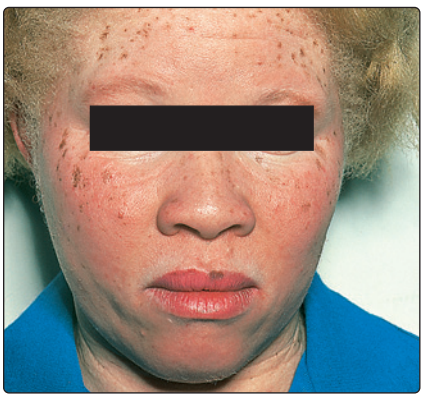


Fig. 39.2 Albinism in a black African patient.

Psychological effect

Vitiligo is a disease from which, in some patients, especially those with a darker skin type, can have a particularly severe psychological effect. This should be recognized and managed in an appropriately sympathetic manner by healthcare professionals, although all too often, doctors, aware that there may be little at their disposal to induce repigmentation, are rather dismissing. This should not happen. All patients with vitiligo should have an assessment of the psychological effects of their disease and be offered appropriate professional support.

Unlicensed treatments are often tried in vitiligo. One new unlicensed treatment described as effective for periocular vitiligo is the use, over 24 weeks, of the topical prostaglandin (licensed for use in glaucoma) bimatoprost (0.03% solution) applied once daily and combined with narrow-band ultraviolet B therapy. *Camouflage advice* is usually part of the overall therapeutic approach in someone with vitiligo. Many hospitals offer their own local service, run by a healthcare professional, but where this cannot be accessed, the British Red Cross (http://www.redcross.org.uk/) has a network of providers.

Albinism is a particular problem in Africa where individuals have suffered discrimination. This has been reported particularly from Tanzania, where the Regional Dermatology Training Centre at Moshi, funded by the International Foundation for Dermatology and others (http://www.ifd.org/), has had a programme to diagnose patients with albinism and to treat them early and efficiently.

Hyperpigmentation is a common response to skin diseases such as eczema in people with a darker skin type (Self-assessment exercise).

Hyperpigmentation

Hyperpigmentation is mostly hypermelanosis (Table 39.2), but sometimes other pigments colour the skin, e.g. iron deposition (with melanin) in haemochromatosis, and carotene (causing an orange discoloration) in carotenaemia, usually due to eating too many carrots.

Freckles and lentigines

Freckles (ephelides) are small, light-brown macules, typically facial, which darken on sun exposure. Lentigines are also brown macules but are scattered and do not darken in the sun. Freckles have normal basal layer melanocyte numbers but increased melanin. Lentigines have an *increased* number of melanocytes.

Table 39.2 **Causes of hyperpigmentation**

Cause	Example
Drugs	Photosensitizers, psoralens, oestrogens, phenothiazines, minocycline, amiodarone
Endocrine	Addison's disease, Cushing's syndrome, Graves' disease
Genetic	Racial, freckles, neurofibromatosis, Peutz–Jeghers syndrome
Metabolic	Biliary cirrhosis, haemochromatosis, porphyria
Nutritional	Carotenaemia, malabsorption, malnutrition, pellagra
Post-inflammatory	Eczema, lichen planus, systemic sclerosis, lichen amyloidosis
Other	Acanthosis nigricans, naevi, malignant melanoma, argyria, chronic renal failure

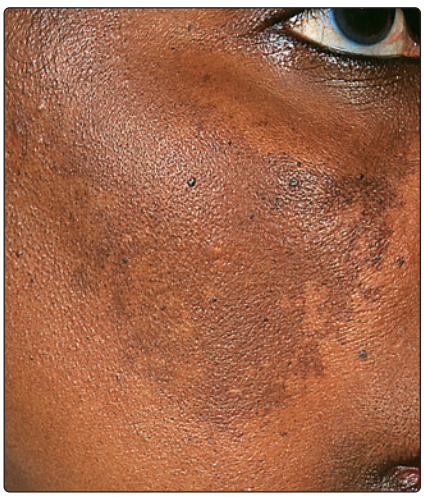


Fig. 39.3 Melasma affecting the cheek and causing a cosmetic disability.

Freckles are common, especially in red-haired children. Lentigines may develop in childhood but are more common in sun-exposed elderly skin. Freckles require no treatment. Lentigines respond to cryotherapy.

Melasma (chloasma)

Melasma is a patterned macular facial pigmentation occurring with pregnancy and in women on oral contraceptives. The pigmentation is symmetrical and often involves the forehead (Fig. 39.3). Pregnancy stimulates melanocytes generally, and also increases pigmentation of the nipples and lower abdomen and in existing melanocytic naevi. Melasma may improve spontaneously. Topical tretinoin, azelaic acid or hydroquinone can reduce pigmentation. Sunscreens and camouflage cosmetics can help.

Peutz–Jeghers syndrome

Peutz–Jeghers syndrome is a rare autosomal dominant condition. Lentigines around the lips (Fig. 39.4), buccal mucosa and fingers are associated with small bowel polyps. The polyps may cause intussusception and rarely undergo malignant change.

Addison's disease

Addison's disease is characterized by hypoadrenalism with pituitary overproduction of adrenocorticotrophic hormone (ACTH). The skin signs are due to excess ACTH, which stimulates melanogenesis. Pigmentation may be generalized or limited to the buccal mucosa (Fig. 39.5), palmar creases, scars, flexures or areas subjected to friction. Addisonian-like pigmentation is also seen in Cushing's syndrome, hyperthyroidism and acromegaly.

Fig. 39.4 The Peutz–Jeghers syndrome showing perioral lentigines.

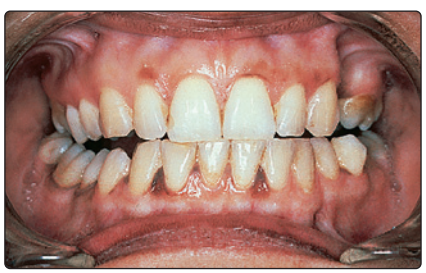


Fig. 39.5 Addison's disease, with hyperpigmentation of the gingival and labial mucosae.

Table 39.3 **Drug-induced pigmentation**

Drug	Effect
Amiodarone	Blue-grey pigmentation of exposed areas (p. 90)
Bleomycin	Diffuse pigmentation, often flexural; flagellate pattern
Busulfan	Diffuse brown pigment
Chloroquine	Blue-grey pigmentation of face and arms
Chlorpromazine	Slate-grey pigment in sun-exposed sites
Clofazimine	Red and black pigment
Mepacrine	Yellow (drug deposited)
Minocycline	Blue-black pigment in scars and sun-exposed sites
Psoralens	Topical or systemic photosensitizers (cosmetics)

Drug-induced pigmentation

Drug-induced pigmentation may be due to stimulation of melanogenesis or deposition of the drug in the skin, but the mechanism is often not well understood (Table 39.3, p. 90). Of the commonly used drugs, amiodarone, phenothiazines and minocycline not infrequently induce pigmentation.

Disorders of pigmentation

- **Vitiligo:** common, autoimmune; well-defined depigmented macules.
- **Albinism:** rare, autosomal recessive; lack of skin and eye pigment; need strict sun avoidance; risk of skin cancer.
- **Phenylketonuria:** autosomal recessive enzyme defect; fair skin and hair.
- **Freckles:** brown macules darken with sun; normal number of melanocytes.
- **Lentigines:** brown macules; melanocyte numbers are increased.
- **Peutz–Jeghers syndrome:** autosomal dominant disorder of perioral lentigines and intestinal polyps.
- **Melasma:** facial pigmentation; related to pregnancy and 'the pill'.
- **Addison's disease:** ACTH-stimulated melanogenesis of mucosae and flexures.
- **Drug-induced pigmentation:** due to deposition of pigment or stimulation of melanogenesis.

Melasma-type facial pigmentation is a major cosmetic problem in women throughout the world (though men are also affected). Treatment is not easy or quick. Lasers have little to offer but some practitioners have used chemical peels.

Patient self-help organizations

The Vitiligo Society (http://www.vitiligosociety.org.uk/) and the National Vitiligo Foundation in the United States (http://mynvfi.org/) are supportive organizations which can offer advice and guidance to patients. The charity, Changing Faces (https://www.changingfaces.org.uk/), is also a useful resource.

Further reading – online sources

The Vitiligo Society and the National Vitiligo Foundation have links to academic sources (access via http://www.vitiligosociety.org.uk and http://mynvfi.org). Information on melanoma is available from the MedicineNet website (access via http://www.medicinenet.com/).

Further reading – textbooks

Hamzavi, I., Mahmoud, B.H., Isedeh, P.N., 2015. Handbook of Vitiligo. Jaypee Brothers Medical Publishers, New Delhi.

National Institute of Skin Diseases, 2015. Vitiligo: Symptoms, Causes, Diagnosis and Effective Treatments. National Institutes of Health, Bethesda, MD (Kindle Edition).

Nordlund, J., Boissy, R., Hearing, V., et al. (Eds.), 2006. The Pigmentary System, second ed. Blackwell, Oxford.

40 Urticaria and angioedema

Urticaria (hives) is a common eruption characterized by transient, usually pruritic, wheals due to acute dermal oedema from extravascular leakage of plasma. Urticaria arising deeper in the dermis and subcutis is known as angioedema. A classification is shown in Table 40.1.

Table 40.1 **Classification of urticaria and angioedema**

Allergic (IgE-mediated) mast cell degranulation	Systemic	Food, drugs, latex (aerosols)
	Skin contact	Animal saliva, pollen, latex
Non-allergic (non-IgE-mediated) mast cell degranulation	Chronic spontaneous	No cause identifiable (commonest subtype)
	Inducible	Dermographism, cold, heat, sweating, vibration, sun exposure, water, delayed pressure
	Pharmacological	Aspirin, opiates, non-steroidal drugs, food additives, ACE inhibitors (p. 81)
	Autoimmune disease	Systemic lupus erythematosus (p. 84), thyroid antibodies, anti-IgE receptor antibodies, urticarial vasculitis (p. 81), acquired angioedema
	Genetic	C1 esterase inhibitor deficiency (p. 81), mastocytosis (p. 120), hereditary periodic fever syndromes
	Other	Infection, paraneoplastic, skin contact (nettle sting)

Aetiopathogenesis

Urticaria is mediated through immune (allergic) or non-immune mechanisms. Lesions result from the release from mast cells of biologically active substances, particularly histamine, which produce vasodilatation and increased vascular permeability. Several pathways are recognized (Table 40.1).

Pathology

The dermis is oedematous with dilatation of vessels and mast cell degranulation. Vessel damage and a lymphocytic infiltrate may be seen with urticarial vasculitis.

Clinical presentation

Three-quarters of cases of urticaria fall into the acute or 'chronic spontaneous' categories. Another 20% are due to dermographism, cholinergic urticaria or physical factors. Other causes are rare. Itchy pink wheals appear as papules or plaques anywhere on the skin surface (Fig. 40.1). Typically, they last for less than 24 h and disappear without a trace. Wheals may be round, annular or polycyclic, and vary in diameter from a few millimetres to several centimetres. Their number ranges from a few to many, depending on the severity of the condition. Angioedema, usually with swelling of the tongue or lips, may occur (Fig. 40.2).

Acute urticaria

The sudden onset of urticaria or angioedema may be due to an IgE-mediated type I reaction and an evolving anaphylactic reaction needs to be considered, especially in asthmatic patients and those with known severe allergies. Sequential measures of raised serum mast cell tryptase support the diagnosis of anaphylactic reactions, but can also be raised in mastocytosis. Culprit allergens are frequently a food (e.g. egg, fish or peanuts), a drug (e.g. an antibiotic) or contact with latex (p. 133). If the condition is recurrent, arising on most days, an allergic trigger is much less likely to be the cause and non-allergic causes should be considered (Table 40.1). In many instances, no cause is found.

Chronic spontaneous urticaria

Urticaria arising most days for >6 weeks is termed 'chronic', in many cases no cause is identified. The condition resolves spontaneously within 6 months in 50% of cases, although a minority are troubled for years.

Inducible (physical) urticarias

Cold, heat, sweating, vibration, sun exposure, pressure and even water can all induce urticaria at the stimulated site. Dermographism, found in 5% of normal people, describes whealing induced by firm stroking of the skin (Fig. 40.3). In a few individuals, it is exaggerated and symptomatic. The wheals in cholinergic urticaria are small, intensely itchy papules that appear in response to sweating, as induced by exercise, heat, emotion or spicy food. The eruption lasts for a few minutes to an hour.

Angioedema alone

- **Angiotensin converting enzyme inhibitors** (ACE-I) are recognized common causes of angioedema without wheals. Treatment should be discontinued, but wheals may arise for many weeks after cessation.
- **Complement pathway defects.** In the absence of ACE-I, angioedema alone (no wheals) is caused by hereditary angioedema or acquired angioedema.
  - **Hereditary angioedema** (low C4, normal C1q) is a rare and potentially fatal autosomal dominant condition. It usually presents in childhood, with episodes of angioedema often with vomiting and abdominal pain. Genetic deficiency or dysfunctional C1 esterase inhibitor (C1-INH) allows complement activation (e.g. caused by trauma) to go unchecked, with an accumulation of vasoactive mediators. Individuals will have low levels of C4 during attacks. Rarely, C1-INH and C4 are normal, and angioedema is induced by a

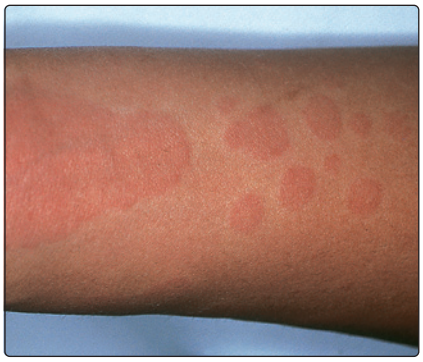


Fig. 40.1 Chronic urticaria. Typical wheals are seen on the forearm.

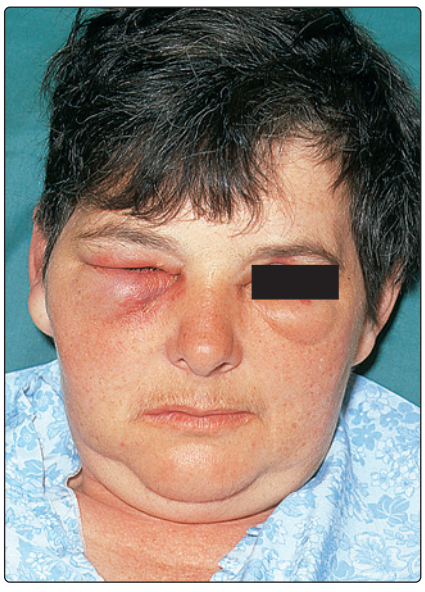


Fig. 40.2 Angioedema involving the face.

Three-quarters of cases of urticaria fall into the acute or 'chronic spontaneous' categories. Another 20% are due to dermographism, cholinergic urticaria or physical factors. Other causes are rare. Itchy pink wheals appear as papules or plaques anywhere on the skin surface (Fig. 40.1 and Fig. e40.1). Typically, they last for less than 24 h and disappear without a trace. Wheals may be round, annular or polycyclic, and vary in diameter from a few millimetres to several centimetres. Their number ranges from a few to many, depending on the severity of the condition. Angioedema, usually with swelling of the tongue or lips, may occur (Fig. 40.2).

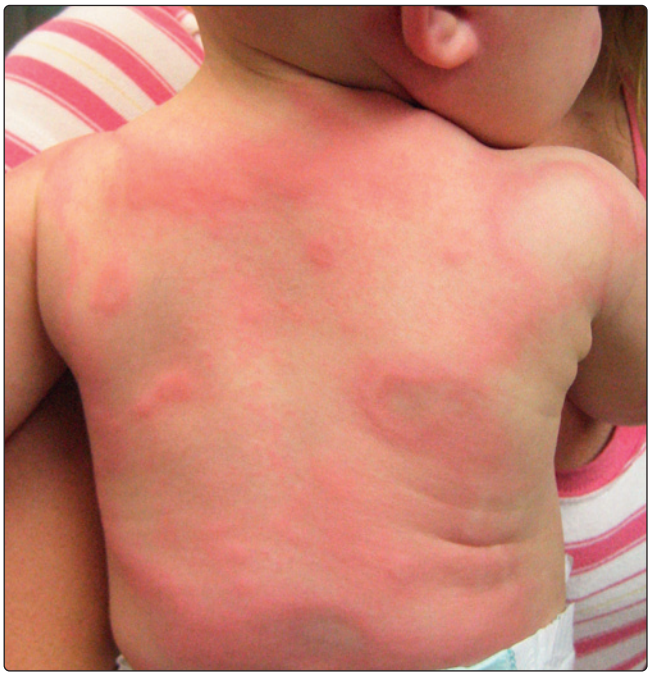


Fig. e40.1 Acute urticaria. Wheals on the back of an infant. Note the polycyclic appearance. *(From Callen JP, Jorizzo JL, Bolognia JL, Piette WW, Zone JJ 2003 Dermatological Signs of Internal Disease, 4th edition. Saunders, with permission.)*

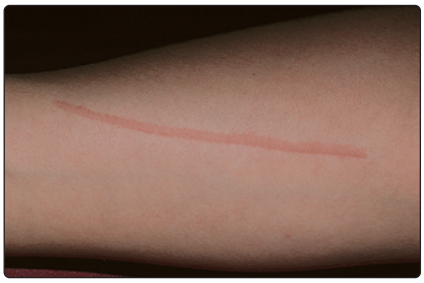


Fig. 40.3 Dermographism. This was induced by stroking the forearm.

mutation in clotting factors giving rise to kallikrein-driven bradykinin production.

- **Acquired angioedema** (low C4, low C1q, low C1-INH) due to consumption or inactivation of C1 esterase inhibitor (e.g. by autoantibodies) will present later in life with identical features to the inherited form, except genetic testing will be negative. Acute attacks are treated with intravenous infusion of C1 esterase inhibitor concentrate. Disease-specific novel synthetic peptide blockers of bradykinin B2 receptors or kallikrein can also be utilized in acute attacks.

Urticarial vasculitis

Urticarial vasculitis often has an acute onset with widespread urticarial lesions that are unusual, as they persist for more than 24 h and fade leaving purpura (Fig. 40.4). Systemic abnormalities and low complement levels may be found. Systemic lupus erythematosus and Sjogren's syndrome need to be excluded.

Autoinflammatory syndromes

Disorders of the IL-1 pathway may result in wheals, termed 'hereditary periodic fever syndromes', and are thought to have been historically underdiagnosed. These rare cases should be suspected in those with chronic urticaria whose onset was at a young age, or associated with recurrent fever, other features of systemic inflammation (e.g. joint pains, bone pain, malaise) or in whom ESR/CRP are raised, or paraproteins present.

Differential diagnosis

Urticaria is usually differentiated from other dermatoses, although pemphigoid (p. 82) or dermatitis herpetiformis (p. 83) occasionally present with an urticarial eruption. Toxic erythema and erythema multiforme (p. 87) may be urticated at first but, when the lesions persist for over 48 h, urticaria can be excluded. Facial erysipelas sometimes resembles angioedema but has a sharper margin and the patient is unwell with a fever.

Investigation

Underlying causes or provoking factors are better revealed by a careful history and examination than by laboratory tests. However, a full blood count, liver function tests, antinuclear antibody test, CRP, ESR and urinalysis are often done to exclude systemic conditions (Table 40.1). Dermographism is demonstrated by firmly stroking the skin, and cold urticaria induced by holding an ice cube on the arm for up to 20 min. C4 levels and C1q can be used as a screening test for angioedema alone.

Management

Any underlying cause should be eliminated. Provoking factors, e.g. aspirin ingestion or swimming (for those with cold urticaria), are to be avoided. However, the mainstay of treatment is with antihistamines.

Antihistamines

Histamine type 1 receptor blockers (H_1 blockers) are usually effective. Non-sedative antihistamines, such as cetirizine 10 mg daily, fexofenadine 180 mg once daily, desloratadine 5 mg once daily or acrivastine 8 mg three times daily, are now preferred unless the sedative qualities of the older preparations are desired. Current European, US and world guidelines suggest that increasing non-sedating antihistamines up to four times (up-dosing) the licensed dose is safe and more effective at controlling symptoms. The addition of an H_2 blocker has only a small summative effect, if any.

Corticosteroids

Oral prednisolone is occasionally used to control severe acute urticaria or angioedema and urticarial vasculitis, but is not indicated for chronic spontaneous urticaria.

Adrenaline (epinephrine)

Acute airway obstruction or anaphylactic shock is treated with IM adrenaline auto-injectors and antihistamine. Intravenous steroids are often given, although their onset of action is delayed by several hours. Emergency transfer to hospital is indicated.

Diet

Salicylates in food aggravate chronic urticaria in up to one-third of cases, and dietary azo dyes and benzoic acid preservatives produce an exacerbation in 10%. Diets low in these compounds are tried if routine measures are ineffective.

Systemic treatment

Montelukast may be beneficial in some cases. Ciclosporin and Omalizumab (anti-IgE) therapy have both been shown to be effective treatments for antihistamine-resistant cases.

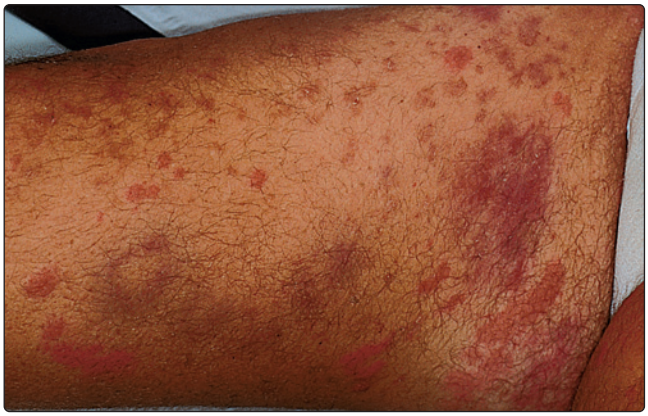


Fig. 40.4 Urticarial vasculitis. Resolving areas have left bruising.

Urticaria and angioedema

- Urticaria is a common eruption of transient pruritic wheals that typically clear within 1 day, and often occurs with angioedema.
- No cause is usually found, but urticaria may result from histamine-releasing IgG autoantibodies, IgE-mediated allergy, physical stimuli, the pharmacological effect of drugs or food additives or complement deficiencies.
- Causative or provoking factors should be eliminated, and non-sedating antihistamines prescribed.
- Systemic steroids are rarely used in treatment. Aspirin is avoided. Intramuscular adrenaline is given for an anaphylactic reaction.
- Antihistamine up-dosing is recommended. Ciclosporin or Omalizumab may be effective in resistant cases.

Urticarial vasculitis often has an acute onset with widespread urticarial lesions that are unusual, as they persist for more than 24 h and fade leaving purpura (Fig. 40.4 and Fig. e40.2). Systemic abnormalities and low complement levels may be found. Systemic lupus erythematosus and Sjogren's syndrome need to be excluded.

Ciclosporin therapy

Ciclosporin directly inhibits T cell activation by blockade of calcineurin signalling, which in turn reduces NFAT relocation to the nucleus and thereby limits synthesis of inflammatory cytokines. Treatment with ciclosporin 3–4 mg/kg per day results in 53–70% improvement in antihistamine resistant urticaria when compared with controls. Use of ciclosporin is limited by adverse reactions, especially nephrotoxicity, which is very common after 1 year of therapy above 2.5 mg/kg per day. Some authors have suggested that it may have disease modification status by altering the natural course of disease and inducing remission.

Omalizumab therapy

Omalizumab is a monoclonal humanized IgG anti-IgE therapy, which binds IgE and removes it from the circulation. Subsequent reductions in IgE are also mirrored by downregulation of expression of the high affinity IgE receptor FcεR1 on mast cells and others. Omalizumab is now licensed for the treatment of chronic spontaneous urticaria (with or without angioedema), but case series suggest it may have a role in inducible and other urticarias. The mechanism of action is not thought to be directly mediated by reducing circulating IgE because individuals with no demonstrable allergic cause and no raised IgE benefit from the therapy. Treatment is optimal with Omalizumab 300 mg s/c every 4 weeks and the treatment is very well tolerated on the whole. Double-blind placebo-controlled studies in antihistamine resistant cases have shown almost complete clearance in 55–66%. The effect is usually rapid, with the majority of responders showing benefit within 1 week. Side-effects are minimal, but headaches, arthralgia, injection site reactions and upper respiratory tract infections are recognized.

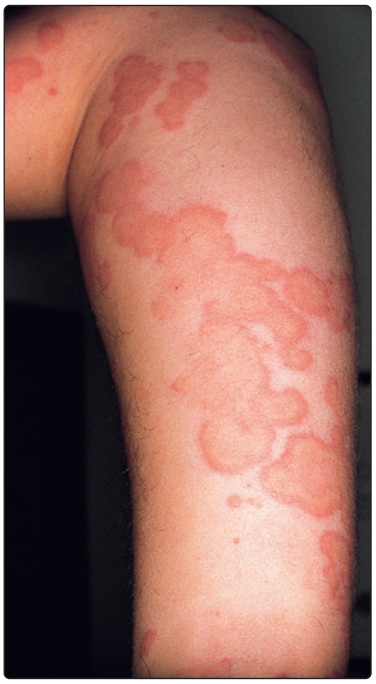
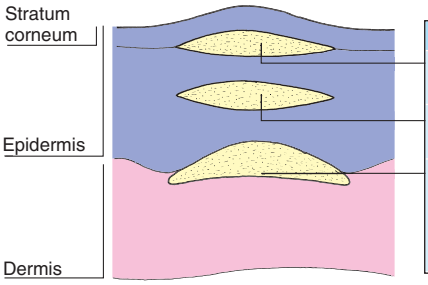


Fig. e40.2 Urticarial vasculitis. Wheals are long lived (2–3 days) and leave post-inflammatory hyperpigmentation. May arise in association with autoimmune connective tissue disease, e.g. SLE. *(From Callen JP, Jorizzo JL, Bolognia JL, Piette WW, Zone JJ 2003 Dermatological Signs of Internal Disease, 4th edition. Saunders, with permission.)*

41 Blistering disorders

Blistering is often seen with skin disease. It is found with common dermatoses such as acute contact dermatitis, pompholyx, herpes simplex, herpes zoster and bullous impetigo, and it also occurs after insect bites, burns and friction or cold injury. The type of blister depends on the level of cleavage: subcorneal or intraepidermal blisters rupture easily, but subepidermal ones are not so fragile (Fig. 41.1). The primary acquired autoimmune bullous disorders, dealt with here, are rare but important, and diagnosis is predominantly based around direct immunofluorescence (p. 135) but newer ELISA-based assays are proving useful (p. 135).



Blister level	Condition
Subcorneal	Bullous impetigo, pustular psoriasis
Intraepidermal	Acute eczema, herpes simplex/ zoster, pemphigus, friction
Subepidermal	Pemphigoid, dermatitis herpetiformis, linear IgA disease, cold and thermal injury, dystrophic epidermolysis bullosa

Fig. 41.1 The level of cleavage in blistering disorders.

Pemphigus

Pemphigus is an uncommon, severe and potentially fatal autoimmune blistering disorder affecting the skin and mucous membranes.

Aetiopathogenesis

Over 80% of patients have circulating immunoglobulin (Ig)G autoantibodies detectable in the serum by indirect immunofluorescence (p. 135), which bind with desmoglein, a desmosomal cadherin involved in epidermal intercellular adhesion. The antibodies, possibly with complement activation and protease release, result in loss of adhesion and an intraepidermal split. Direct immunofluorescence shows the intercellular deposition of IgG in the suprabasal epidermis. Pemphigus is associated with other organ-specific autoimmune disorders such as myasthenia gravis.

Clinical presentation

In Europe, pemphigus is much less common than pemphigoid, and tends to affect middle-aged or young adults. Oral erosions signal the onset of *pemphigus vulgaris* in 50–70% of patients and often precede cutaneous blistering by months. Flaccid superficial blisters develop over the scalp, face, back, chest and flexures. The blistering is not always obvious, and lesions may consist of crusted erosions. Untreated, the blistering is progressive and, prior to the introduction of steroids, three out of four patients died within 4 years, usually from uncontrolled fluid and protein loss or secondary infection.

Less common variants include *pemphigus foliaceus*, in which shallow erosions appear on the scalp, face and chest (Fig. 41.2), and *pemphigus vegetans*, in which pustular and vegetating lesions affect the axillae and groins. In Brazil, an endemic form of pemphigus foliaceus, *fogo selvagem*, seems to be induced by an infective agent. *Paraneoplastic pemphigus* describes a variant associated with underlying malignancy.

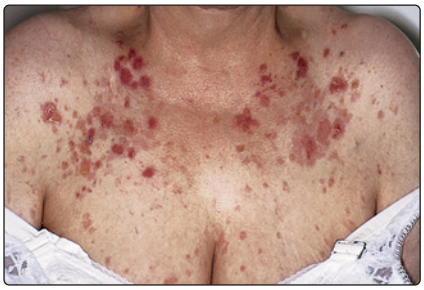


Fig. 41.2 Pemphigus foliaceus showing blisters and erosions on the chest.

Differential diagnosis

Aphthous ulcers or Behçet's disease can simulate the oral erosions of pemphigus. Cases with rapid onset need to be differentiated from toxic epidermal necrolysis. Widespread skin erosions may suggest epidermolysis bullosa or pemphigoid. The diagnosis relies on the histological examination of a bulla and direct immunofluorescence.

Management

Systemic steroids and other immunosuppressive agents are required. Prednisolone is given initially in a high dose (1.0–1.5 mg/kg daily), often with azathioprine or cyclophosphamide. Once blistering is controlled, the steroid dosage can be lowered. Treatment usually needs to be continued for years, although remission occurs occasionally. Mortality and morbidity are now more likely to be due to side-effects of the steroid and immunosuppressive therapy than to the disease itself. Recent reports have shown depletion of B cells with rituximab (anti-CD20) monoclonal antibody therapy to be useful in this condition.

Pemphigoid

Pemphigoid is a chronic and not uncommon blistering eruption in the elderly.

Aetiopathogenesis

IgG autoantibodies to bullous pemphigoid antigens BP230 and BP180 in the hemidesmosomes at the basement membrane zone (p. 3) bind complement, which induces inflammation and protease release, leading to subepidermal bulla formation. The IgG and C_3 are detected by direct immunofluorescence (p. 135). Indirect methods demonstrate circulating autoantibodies in 75% of cases.

Clinical presentation

Bullous pemphigoid usually affects the elderly. Tense large blisters arise on red or normal-looking skin, often of the limbs, trunk and flexures (Fig. 41.3). Oral lesions occur in only 10% of cases. A pruritic urticarial eruption may precede the onset of blistering. Pemphigoid is sometimes localized to one site, often the lower leg. The differential diagnosis of pemphigoid may include dermatitis herpetiformis, linear IgA disease or pemphigus. Immunofluorescence and histology reveal the diagnosis.

Cicatricial pemphigoid mainly affects the ocular and oral mucous membranes. Scarring results, and this can cause serious eye problems. *Pemphigoid (herpes) gestationis* is a rare but characteristic, intensely itchy bullous eruption associated with pregnancy, which remits after the delivery but can recur during subsequent pregnancies.

Management

Pemphigoid responds to a lower dose of steroids than pemphigus: 0.5 mg/kg daily of oral prednisolone is usually sufficient, and this can normally be reduced to below 15 mg within weeks. Azathioprine is sometimes also prescribed. The disease is self-limiting in many cases, and

Less common variants (than Pemphigus vulgaris – see Figs e41.1 and e41.2) include *pemphigus foliaceus*, in which shallow erosions appear on the scalp, face and chest (Fig. 41.2), and *pemphigus vegetans*, in which pustular and vegetating lesions affect the axillae and groins. In Brazil, an endemic form of pemphigus foliaceus, *fogo selvagem*, seems to be induced by an infective agent. *Paraneoplastic pemphigus* describes a variant associated with underlying malignancy.

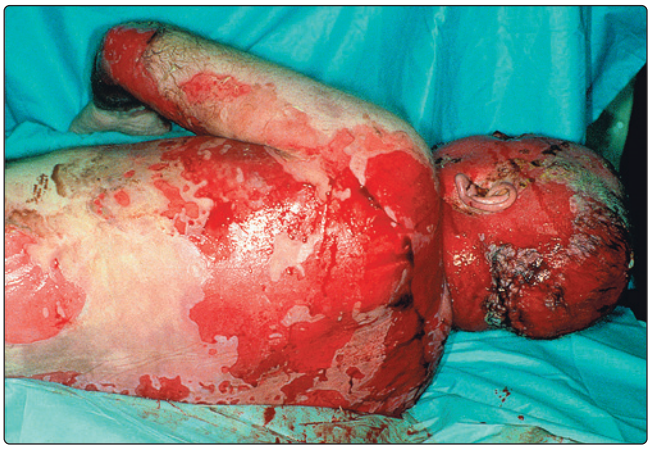


Fig. e41.1 Pemphigus vulgaris. Note the lack of tense bullae. Instead, this patient has extensive erosions caused by epidermal fragility, which is characteristic of pemphigus vulgaris. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

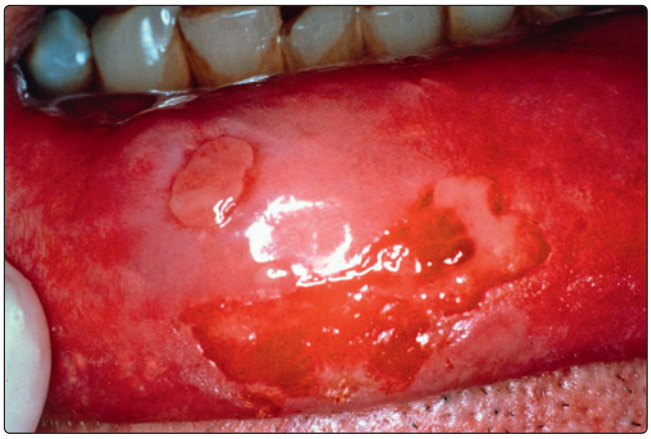


Fig. e41.2 Pemphigus vulgaris of the oral mucosa. Mucosal blistering is frequent and often extensive in pemphigus vulgaris but is much less evident in bullous pemphigoid or pemphigus foliaceus. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

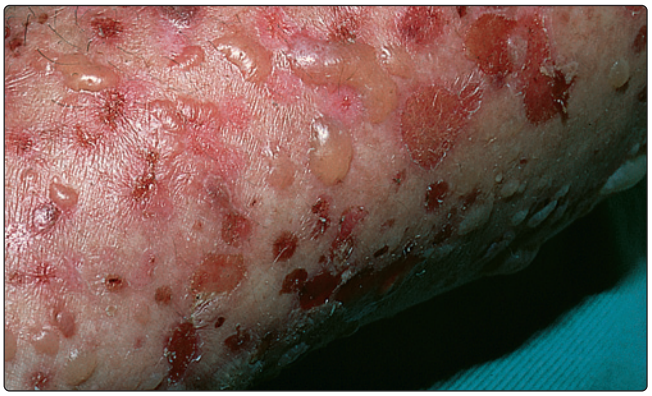


Fig. 41.3 Bullous pemphigoid. Tense blisters on an arm.

steroids can often be stopped after 2–3 years. Cicatricial pemphigoid does not respond so well, but pemphigoid gestationis is controlled by standard doses. Steroid-induced side-effects may be a problem, especially in the elderly.

Dermatitis herpetiformis

Dermatitis herpetiformis (DH) is an uncommon eruption of symmetrical itchy blisters on the extensor surfaces. Jejunal villus atrophy is an associated finding in most cases.

Aetiopathogenesis

DH is characterized by the finding of granular IgA at the dermal papillae on immunofluorescence, and by the response of the skin lesions (and the villus atrophy seen in over 75% of patients) to a gluten-free diet. Despite this, the cause of the eruption – and its relationship to the undoubted gluten sensitivity of both the gut and the skin – remains unclear. It is doubtful whether the IgA induces the itch, as it is present in asymptomatic patients.

Clinical presentation

DH usually presents in the third or fourth decade and is twice as common in males as in females. The classical onset is with groups of small, intensely itchy vesicles on the elbows, knees, buttocks and scalp (Fig. 41.4). The blisters are often broken by scratching to leave excoriations. Although most patients have small bowel villus atrophy, symptoms of gastrointestinal disturbance and malabsorption are uncommon.

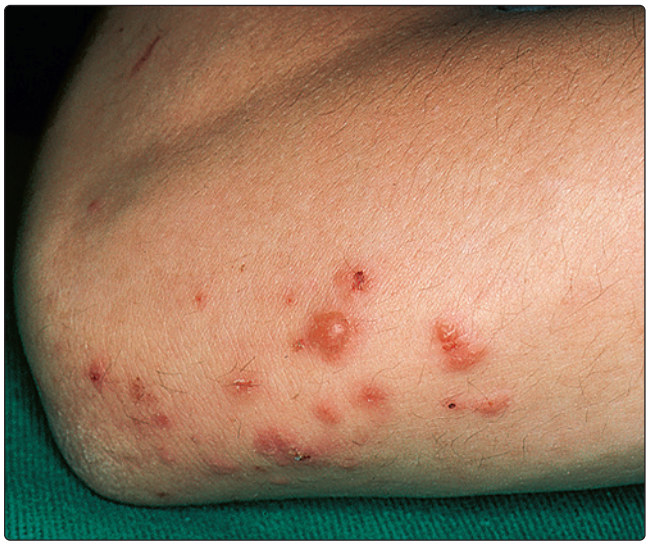


Fig. 41.4 Dermatitis herpetiformis. Itchy blisters on an elbow.

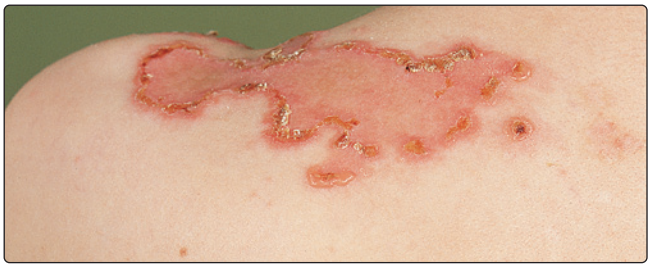


Fig. 41.5 Linear IgA disease. A figurate lesion with peripheral blisters.

A haemolytic anaemia may occur with dapsone. Regular blood counts are necessary.

Linear IgA disease

Linear IgA disease is a rare heterogeneous condition of blisters and urticarial lesions on the back or extensor surfaces (Fig. 41.5). The disorder responds to dapsone and may resemble DH or pemphigoid. Direct immunofluorescence reveals linear IgA at the basement membrane. In the childhood variant, blisters occur around the genitalia. Linear IgA disease induced by medication (commonly vancomycin) is well recognized.

Differential diagnosis

Distinction from scabies, eczema and linear IgA disease is important. Biopsy shows a subepidermal bulla, and direct immunofluorescence of normal-looking skin demonstrates granular IgA at the dermal papilla (p. 135). The small bowel can be investigated by jejunal biopsy. Serum folate, vitamin B12 and ferritin estimates detect any biochemical malabsorption. Anti-endomysial antibodies are present.

Management

A gluten-free diet is the treatment of choice, as this corrects both the bowel and the skin lesions. Dapsone (50–200 mg daily) will control the eruption and is often given until the gluten-free diet has its beneficial effect.

Blistering disorders

Disorder	Clinical details	Direct (and indirect) immunofluorescence	Treatment
Bullous pemphigoid (BP)	Not uncommon, seen in elderly, limbs>trunk, oral lesions rare, tense blisters often seen	Linear IgG at basement membrane zone (to hemidesmosome BP antigens), indirect 75% positive	Modest dose of oral prednisolone with or without azathioprine
Pemphigus vulgaris	Rare, middle-aged affected, trunk>limbs, often starts with oral lesions, flaccid blisters may be seen	Intercellular epidermal IgG (to desmoglein in desmosomes), indirect 80% are positive	High dose of oral prednisolone and azathioprine or other immunosuppressive
Dermatitis herpetiformis	Young adults (M>F), extensor surfaces show itchy blisters, villus atrophy is usual	Granular IgA at dermal papilla (exact antigen is unknown), indirect test is negative	Gluten-free diet with or without dapsone

Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita (EBA) is rare. The antibodies bind sub-epidermal antigens and target type VII collagen. On direct immunofluorescence this gives rise to binding of the basement membrane in a similar manner to bullous pemphigoid, requiring identification of dermal binding on salt-split skin to distinguish the disorders. Indeed, the condition shares many features with bullous pemphigoid and clinical differentiation may be difficult. EBA usually presents in adulthood and may show inflammatory tense bullae, as with bullous pemphigoid. However, more typically, EBA shows non-inflammatory skin fragility and blistering with subsequent atrophic scarring. Characteristic sites of involvement are areas prone to trauma, especially hands, feet and extensor surfaces (Fig. e41.3). Milia are typical. Scarring alopecia is also recognized, and mucosal and ocular lesions less common. The disease has been associated with inflammatory bowel disease but the precise reason remains unclear. Treatment of EBA is challenging but standard autoimmune bullous disorder therapies are utilized, including systemic corticosteroids, azathioprine, dapsone and occasionally more potent immunosuppression, including cyclophosphamide.

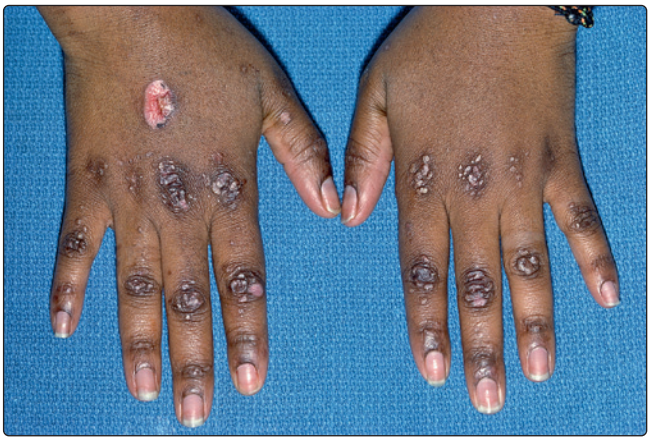


Fig. e41.3 Epidermolysis bullosa acquisita. The figure shows scarring from blisters arising at sites of increased trauma (knuckles), with an erosion from an acute blister on the dorsal right hand. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

42 Connective tissue diseases

The inflammatory disorders of connective tissue often affect several organs, as in systemic lupus erythematosus (LE), but they may also involve the skin alone (e.g. discoid LE). Autoantibodies are a feature of these diseases, which can thus be regarded as 'autoimmune'.

Lupus erythematosus

Lupus erythematosus represents a spectrum of cutaneous disease from scarring (discoid) to multisystem (systemic).

Pathology

Discoid lesions show epidermal atrophy, hyperkeratosis and basal layer degeneration. Subacute lesions show greater atrophy but the other features are less evident. Systemic lesions have similar changes with dermal oedema and fibrinoid change, inflammatory infiltrate and sometimes vasculitis. Direct immunofluorescence shows a 'lupus band' at the dermoepidermal junction in lesional systemic and discoid LE, but this is also found in approximately 20% of healthy individuals on sun-exposed skin.

Clinical presentation

Systemic lupus erythematosus (99% ANA, 50% Ro, 60% dsDNA-positive)

Skin signs are found in 80%. The facial butterfly eruption (Fig. 42.1) is characteristic, but photosensitivity, discoid lesions, diffuse alopecia, mouth lesions and vasculitis also occur. Multisystem involvement with serological or haematological abnormalities must be demonstrated to diagnose systemic LE (Table 42.1). The female : male ratio is 8 : 1.

Subacute lupus erythematosus (60% ANA, 80% Ro, <5% dsDNA-positive)

The skin involvement is usually on the neck, trunk and arms. The erythema is non-scarring and may be papulosquamous or annular and resolves with hypopigmentation and telangiectasia. Mouth ulceration, livedo reticularis, periungual telangiectasia and Raynaud's phenomenon may also be noted. Multisystem involvement can be seen, but is usually mild.

Discoid lupus erythematosus (35% ANA, 2% Ro, <5% dsDNA-positive)

One or more round or oval plaques appear on the face, scalp or hands (Fig. 42.2). The lesions are well demarcated, red, atrophic, scaly and show keratin plugs in dilated follicles. Scarring leaves alopecia on the scalp and hypopigmentation in those with a pigmented skin. Remission occurs in over 50%. Internal involvement is not a feature, and only 6% develop systemic LE. Women outnumber men by 2 : 1.

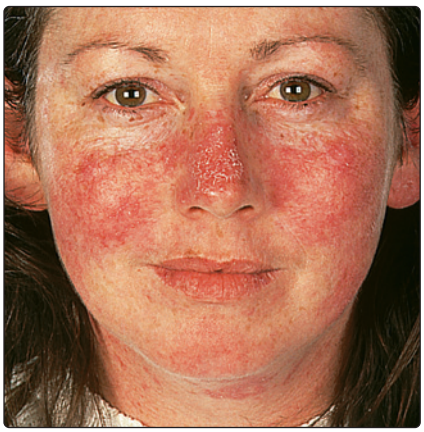


Fig. 42.1 Systemic lupus erythematosus (LE). The typical butterfly eruption is present on the face.

Table 42.1 **Organ involvement in systemic LE**

Organ	Involvement
Skin	Photosensitivity, facial rash, vasculitis, hair loss, Raynaud's phenomenon
Blood	Anaemia, thrombocytopenia
Joints	Arthritis, tenosynovitis, calcification
Kidney	Glomerulonephritis, nephrotic syndrome
Heart	Pericarditis, endocarditis, hypertension
Central nervous system	Psychosis, infarction, neuropathy
Lungs	Pneumonitis, effusion

Other forms

Neonatal LE is due to the placental transfer of anti-Ro antibodies and presents as an annular atrophic eruption, sometimes with heart block.

Differential diagnosis

Discoid LE can usually be differentiated from other facial rashes such as rosacea, seborrhoeic dermatitis, lupus vulgaris or psoriasis. A biopsy should be performed. The photosensitive eruption of systemic LE may resemble polymorphic light eruption, dermatomyositis or drug reaction.

Management

Immunological screening is important for diagnosis and to predict complications (e.g. anti-Ro and congenital heart block; anticardiolipin and thromboses and spontaneous abortions; antihistone and drug-induced lupus). Discoid LE usually responds to potent or very potent topical steroids which, in this instance, can be applied to the face. Sunblock creams are essential. Widespread disease may need systemic therapy with hydroxychloroquine; the small risk of retinopathy demands monitoring of visual acuity. Thalidomide is an effective treatment of cutaneous LE. The treatment of systemic LE depends on the type of involvement. Sunscreens reduce photosensitivity but, if there is internal disease, antimalarials and systemic steroids are required, often with immunosuppressive agents including azathioprine and mycophenolate mofetil. Rituximab is effective.

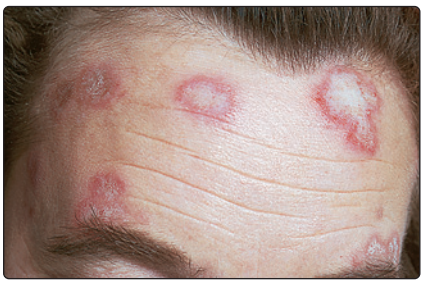


Fig. 42.2 Discoid LE on the forehead.

Systemic sclerosis

Systemic sclerosis (scleroderma) is an uncommon, progressive multisystem disease in which collagen deposition and fibrosis occur in several organs.

Clinical presentation

A total of 90–95% of cases are ANA-positive. Raynaud's phenomenon (p. 74.e1) is frequently the presenting sign. The skin of the fingers, forearms and lower legs becomes tight, waxy and stiff, and the finger pulps are resorbed (Fig. 42.3). Facial signs include perioral furrowing, telangiectasia (Fig. 42.4) and restricted mouth opening. When limited to the distal extremities and the face, the condition has a better prognosis and is described as 'limited' disease (10% anti-Scl-70, 70% anti-centromere-positive). Internal organ involvement, e.g. renal failure, is seen earlier and more common in 'diffuse' disease (50% anti-Scl-70, 20% anti-centromere-positive) (Table 42.2). Women are affected more than men (F : M ratio 4 : 1). The diagnosis is rarely in doubt in diffuse disease, although chronic graft-versus-host disease shows similar changes. Limited cutaneous

Other connective tissue diseases

A variety of other connective tissue diseases are recognized and associated primarily by their frequent involvement of the joints. In addition, 'mixed connective tissue disease', which describes cases with overlap of common conditions such as systemic lupus erythematosus, systemic sclerosis and dermatomyositis, is gaining recognition as a distinct entity (Fig. e42.1).

Idiopathic arthritis including Still's disease (juvenile and adult-onset) (ANA negative)

Juvenile onset idiopathic arthritis is a spectrum of disorders characterized by arthritis ± enthesitis, which usually affects joints in a symmetrical pattern and arises before adolescence. Of these disorders, it is Still's disease (now called 'systemic onset juvenile idiopathic arthritis', SoJIA) rash which is most prominent. SoJIA presents with a transient asymptomatic exanthematous rash in 90% of cases. Other clinical features include intermittent daily fevers (>39°C) and polyarticular arthritis of knees, ankles, hips and later involving the hands. Approximately half of all cases resolve spontaneously within 6 months. Others may suffer a chronic course. Investigations reveal an inflammatory state with elevated CRP, ESR, ferritin and platelet count. Treatment with non-steroidal antiinflammatory drugs ± hydroxychloroquine may be effective, but others may require methotrexate of anti-TNF inhibitors.

Adult onset Still's disease is also characterized by an asymptomatic transient exanthematous rash in association with intermittent daily fever (>39°C). In white skin, the rash is salmon pink in colour and more commonly affects the trunk. Arthritis occurs in most cases (~70%) and affects the knees, ankles and hips. Carpal-ankylosis is common. Involvement of internal organs is well recognized and commonly includes hepatomegaly, but pulmonary, cardiac and renal inflammation are rare. Investigations reveal an inflammatory state with elevated CRP, ESR, ferritin and platelet count. Treatment with non-steroidal antiinflammatory drugs or oral prednisolone is usually effective. However, more severe cases may require methotrexate or inhibitors of the IL-1 or IL-6 pathways.

Relapsing polychondritis (ANA negative)

Relapsing polychondritis is an autoimmune condition which targets type II collagen. This results in erythema, swelling and pain in the cartilaginous anatomical sites. Typically, the earliest involved area is the ear (sparing the earlobe), which is followed by nasal cartilage and then sternum, larynx, trachea and bronchi. Arthritis and ocular involvement may also follow, with other organ involvement less common. Cartilage destruction leads to loss of anatomy, which is prominent with the ear and nose (saddle deformity). The diagnosis is made by characteristic histology, the involvement of classical sites and inflammatory complications of the eye, ear or joints. Treatment with non-steroidal antiinflammatory drugs or oral prednisolone is usually effective.

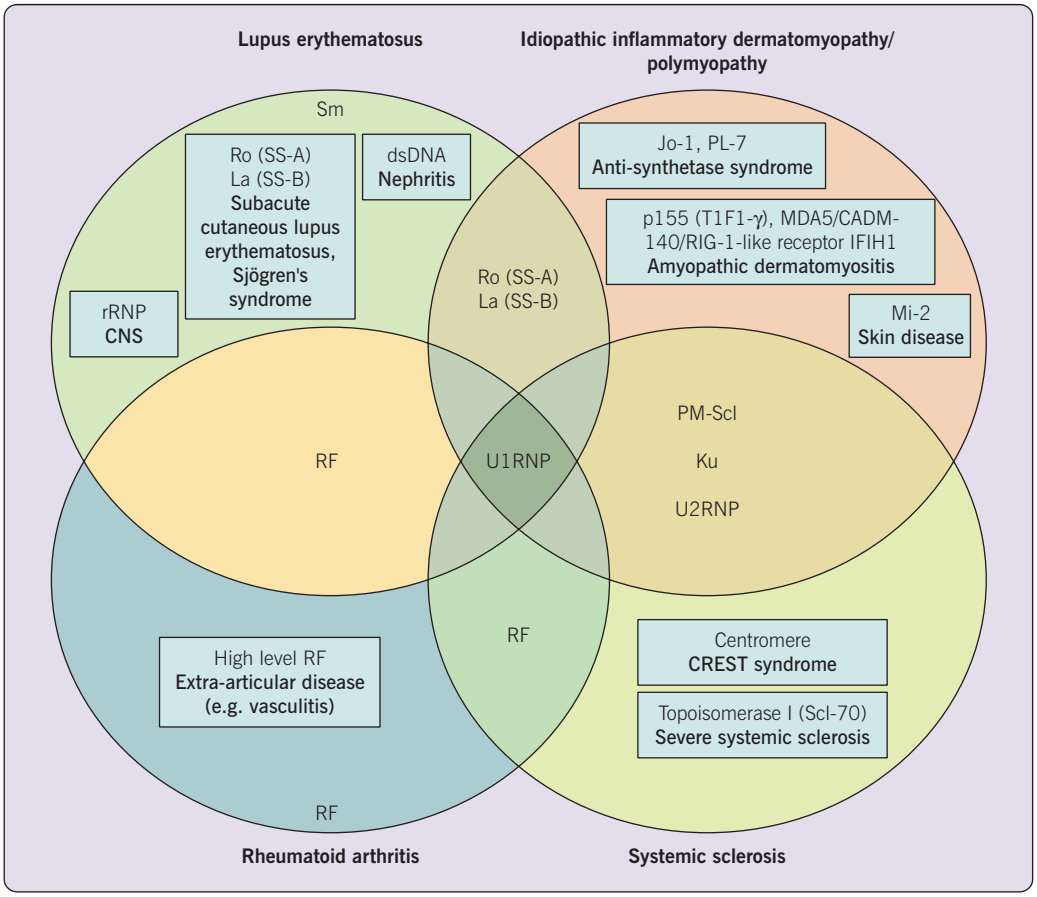


Fig. e42.1 Correlation between clinical and serological manifestations of autoimmune connective tissue diseases (AI-CTD).
(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)

Sjögren's syndrome (SjS; anti-Ro ~70%; anti-La ~50%)

The hallmark of SjS is the autoimmune damage to secretory glands. This gives rise to the classical features of the condition: dry eyes, mouth and vagina. Xerophthalmia can lead to keratitis, ulceration and infection. Xerostomia may be associated with soreness and difficulty with swallowing. Transient parotid enlargement is a common finding, but the increased risk of lymphoma should be considered if enlargement of lymph nodes is identified. Skin changes can be minimal, but generalized dryness and itch is common; small vessel vasculitis may be seen. Arthritis is common and is non-erosive. Treatment is generally conservative, with artificial tears and artificial saliva. Hydroxychloroquine and systemic immunosuppression may be required for severe cases.

Aetiopathogenesis

There is increasing evidence that the induction of autoantibodies against self-proteins are derived from an impaired ability to clear dying (apoptotic) cells. Both genetic (human leucocyte antigen, HLA) and environmental (toxins, drugs, UV radiation, viruses) factors have been implicated in disease pathogenesis.

systemic sclerosis has a better prognosis and usually affects only the neck, forearms and lower legs. A subset of 'limited' disease known as CREST syndrome, describes *C*alcinosis, *R*aynaud's phenomenon, o*E*sophageal dysmotility, *S*clerodactyly and *T*elangiectasia.

Management

Treatment is mainly supportive. Nifedipine and sildenafil can help Raynaud's phenomenon. Hypertension is controlled. Systemic steroids, penicillamine and immunosuppressives have been used with little benefit. Photopheresis may be tried (p. 113). Renal crises (associated with anti-RNA polymerase I and III antibodies) should be managed aggressively with angiotensin converting enzyme (ACE) inhibitors.

Morphoea

Morphoea consists of localized scleroderma without internal disease. The cause is unknown, although it may follow trauma. Histology shows bands of collagen with loss of appendages. ANA is usually negative.

Morphoea presents with round or oval plaques of induration and erythema, often with a purplish edge (Fig. 42.5). These become shiny and white, eventually leaving atrophic hairless pigmented patches. The trunk or proximal limbs are affected. Morphoea is more common in women (F:M ratio 3:1). *Linear morphoea* may involve the face or a limb and, when seen in a child, can retard growth of the underlying tissues, including bone. There is no well-established treatment, although topical steroids are often given. The disease usually resolves spontaneously within months to years.

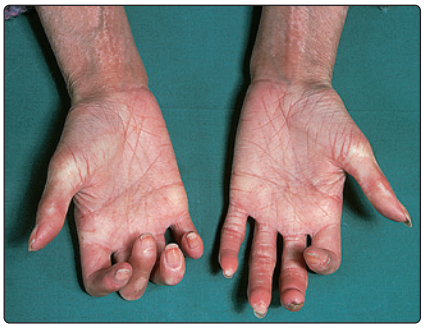


Fig. 42.3 Systemic sclerosis. Note the tightly bound waxy skin on the fingers (sclerodactyly) and resorption of the finger pulps.

Table 42.2 **Organ involvement in systemic sclerosis**

Organ	Involvement
Skin	Raynaud's phenomenon, calcinosis, sclerodactyly, telangiectasia
Gut	Oesophageal dysmotility, malabsorption, dilated bowel
Lung	Fibrosis, pulmonary hypertension
Heart	Pericarditis, myocardial fibrosis
Kidney	Renal failure, hypertension
Muscle	Myositis, tendon involvement

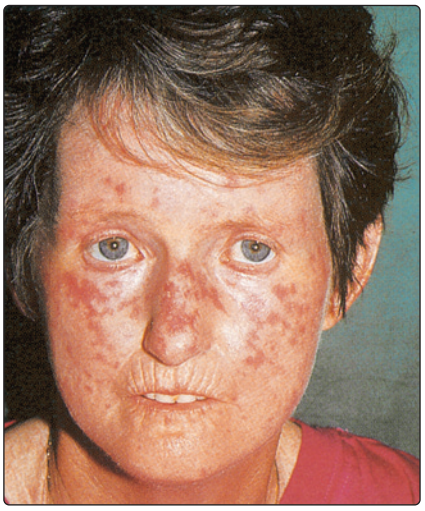


Fig. 42.4 Systemic sclerosis of the face. Telangiectasia and furrowing around the mouth are prominent changes.

Dermatomyositis

Dermatomyositis is an uncommon disorder in which inflammation of skin, muscle and blood vessels gives a distinctive eruption, with muscle weakness of varying severity. The cause is unknown but an underlying malignancy is found in a subgroup.

Clinical presentation

In dermatomyositis/polymyositis, skin changes or muscle weakness may predominate. The typical eruption is a lilac–blue discoloration around the eyelids, cheeks and forehead, often with oedema. Bluish–red papules or streaks on the dorsal aspects of the hands (Fig. 42.6), elbows and knees are seen, sometimes with pigmentation and nail fold telangiectasia. Photosensitivity is common. There is no strong association with autoantibodies, although anti-Jo-1 antibodies predict lung involvement. An association with malignancy exists in patients over 40 years, 40% of whom have an underlying tumour, usually of the lung, breast or stomach. A childhood variant mainly affects the muscles and causes calcinosis and contractures.

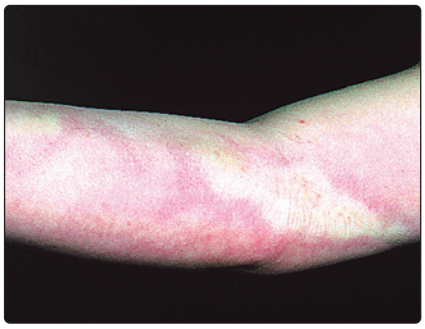


Fig. 42.5 Morphoea. Seen here on the arm of a child. The white indurated plaque has an erythematous edge.

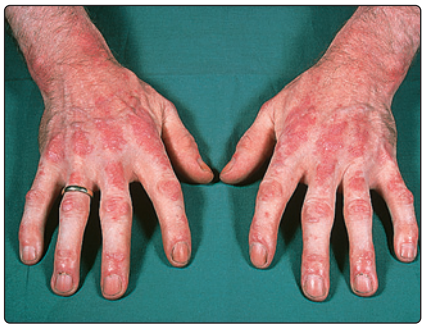


Fig. 42.6 Dermatomyositis. A streaky eruption is seen on the dorsal aspects of the hands (Gottron's papules) with nail fold inflammation.

Management

Investigations must define the degree of myositis and, in adults, exclude the possibility of underlying neoplasia. Treatment is with systemic steroids in moderate to high dosage, often with an immunosuppressive such as azathioprine or methotrexate. Immunoglobulin infusion and possibly photopheresis (p. 113) may help.

Connective tissue diseases

- **Systemic LE** is an autoimmune, multisystem disease, in which a butterfly rash, photosensitivity, vasculitis and alopecia may be seen. Treatment depends on the type and degree of involvement and often includes systemic steroids and immunosuppressive agents.
- **Subacute LE** is a less aggressive form of LE with predominantly cutaneous features.
- **Discoid LE** is confined to the skin. Scaly atrophic plaques and scarring alopecia are found. Topical steroids and sunscreens are helpful. Sometimes, systemic therapy, e.g. with hydroxychloroquine, is used.
- **Systemic sclerosis** is a serious multisystem disorder. Sclerodactyly, Raynaud's phenomenon, telangiectasia and calcinosis are seen.
- **Morphoea** is characterized by white indurated plaques, usually on the trunk and proximal limbs. In children, it may retard growth of underlying tissues, producing atrophy. In adults, the condition is generally self-limiting.
- **Dermatomyositis** is an autoimmune inflammation of skin and muscle. The skin signs are a lilac–blue discoloration around the eyelids and red streaks on the dorsa of the hands. Exclude underlying malignancy in those over 40 years of age.

Aetiopathogenesis

Dysregulated transforming growth factor (TGF)-β-induced fibroblast overproduction of collagen is central to tissue fibrosis. However, endothelial cell damage by T cells and macrophages may also be important.

43 Vasculitis and the reactive erythemas

Vasculitis and the reactive erythemas are characterized by inflammation within or around blood vessels. This may result from a type III hypersensitivity response, with circulating immune complexes, but other mechanisms are also possible.

Vasculitis

Vasculitis is a disease process usually centred on small or medium-sized blood vessels. It is often due to circulating immune complexes (CICs).

Aetiopathogenesis

The CICs, which may be associated with several conditions (Table 43.1), lodge in the vessel wall, where they activate complement and cytokine release, attract polymorphs and damage tissue. Inflammatory cells infiltrate vessels. Endothelial cells may show swelling, fibrinoid change or necrosis.

Clinical presentation

This depends on the size and site of the vessels involved. Vasculitis may be confined to the skin, or may be systemic and involve the joints, kidneys, lungs, heart, gut and nervous system. The skin signs are of palpable purpura, often painful and usually on the lower legs or buttocks (Fig. 43.1). Specific types are as follows:

- *Cutaneous small vessel vasculitis* is defined by palpable purpura, usually on the lower legs. IgA deposition at the basement membrane (*Henoch–Schönlein purpura)* often follows a streptococcal infection, occurs in approximately 50% and is associated with internal involvement (arthritis, abdominal pain and haematuria) and mainly affects children. IgG/IgM CICs are unlikely to be associated with systemic involvement.
- *Microscopic polyangiitis* (granulomas around vessels, p-ANCA positive), *Churg–Strauss syndrome* (no granulomas, p-ANCA positive, with eosinophilia and asthma) and *Granulomatosis with polyangiitis (GPA)* (previously Wegener's granulomatosis) are rare, commonly affect internal organs and present with systemic signs, nodules and palpable purpura, often with necrosis.
  - *GPA* is a potentially fatal granulomatous vasculitis of unknown cause. Malaise, upper and lower respiratory tract necrosis, glomerulonephritis and, in 40% of cases, a cutaneous vasculitis are found. Classical antineutrophil cytoplasm antibodies (c-ANCA) directed at proteinase 3 (PR3) are present.
- *Polyarteritis nodosa* (ANCA negative) is characterized by a necrotizing vasculitis in medium-sized arteries and may be associated with hepatitis B. It is uncommon and afflicts middle-aged men who, in addition to tender subcutaneous nodules along the line of arteries, may develop hypertension, renal failure and neuropathy. Variants confined to the skin with livedo and nodules, predominantly on the lower legs, are known as cutaneous PAN or cutaneous arteritis and do not involve internal organs.
- *Giant cell arteritis* affects medium-sized arteries in the elderly. Patients present with scalp tenderness due to temporal artery involvement that can progress to scalp necrosis. Treatment is prednisolone. Visual loss may result if untreated.

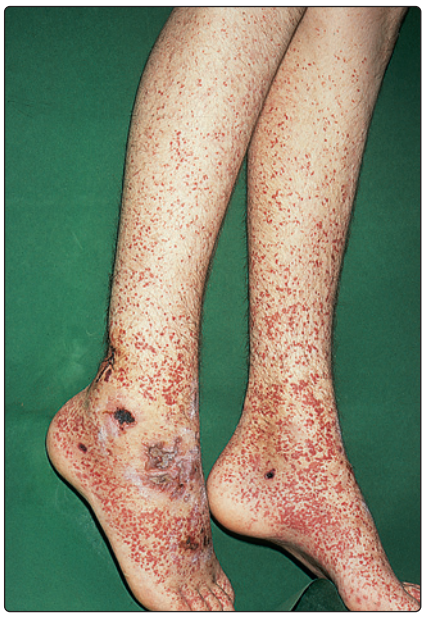


Fig. 43.1 Vasculitis with purpura and impending skin necrosis.

Table 43.1 **Causes of vasculitis**

Group	Example
Idiopathic	50% of cases (no cause found)
Blood disease	Cryoglobulinaemia
Connective tissue disease	Systemic lupus erythematosus, rheumatoid arthritis
Drugs	Antibiotics, diuretics, non-steroidals, anticonvulsants, allopurinol, cocaine
Infections	Hepatitis B, streptococci, *Mycobacterium leprae*, *Rickettsia*
Neoplasia	Lymphoma, leukaemia
Other	Wegener's granulomatosis, giant cell arteritis, polyarteritis nodosa

Non-immune complex causes of palpable purpura need exclusion and include paraproteins, cryoglobulins (e.g. with hepatitis C), systemic lupus and Sjogren's syndrome.

Management

The cause is identified and remedied if possible. Some idiopathic cases settle with bed rest but, if lesions continue to develop and if internal organs are involved, treatment is indicated. Dapsone, 100 mg daily, is often effective for cutaneous vasculitis. Otherwise, prednisolone (sometimes with an immunosuppressive) is prescribed. Giant cell arteritis, polyarteritis nodosa and GPA nearly always require oral steroids and immunosuppression.

Erythema multiforme

Erythema multiforme is an immune-mediated disease, characterized by target lesions on the hands and feet. It has a variety of causes (Table 43.2).

Aetiopathogenesis

Cell-mediated immunity seems to be involved. CICs are also present and can be demonstrated in blood vessels. No provoking factor is found in 50% of cases. On histology, the epidermis is necrotic and the dermis shows oedema, an inflammatory infiltrate and vasodilatation.

Clinical presentation

Typical target lesions, seen on the hands and feet, consist of red rings with central pale or purple areas, which may blister (Fig. 43.2). Involvement of the oral,

Table 43.2 **Causes of erythema multiforme**

Group	Cause
Idiopathic	50% of cases (no cause found)
Viral	Herpes simplex, hepatitis B, orf, adenovirus, mumps, *Mycoplasma*
Bacterial	Streptococci, *Rickettsia*
Fungal	Coccidioidomycosis, histoplasmosis
Drugs	Antibiotics, phenytoin, non-steroidals
Other	Lupus erythematosus (p. 84), pregnancy, malignancy

Typical target lesions, seen on the hands and feet, consist of red rings with central pale or purple areas, which may blister (Fig. 43.2 and Fig. e43.1). Involvement of the oral, conjunctival and genital mucosae is not uncommon and, if extensive, is known as erythema multiforme major. Crops of new lesions appear for 2–3 weeks. The differential diagnosis includes drug induced exanthem (p. 90), Stevens–Johnson syndrome, toxic epidermal necrolysis, Sweet's disease, urticaria and pemphigoid. A biopsy is often helpful. *Toxic epidermal necrolysis* (p. 91) may sometimes represent erythema multiforme in a severe form.

Sweet's disease (*acute febrile neutrophilic dermatosis*) occurs as raised plum-coloured plaques on the face or limbs (Fig. 43.4 and Fig. e43.2), typically with fever and a raised neutrophil count. It is not a true vasculitis but results from polymorph infiltration of the dermis. Leukaemia, ulcerative colitis and other disorders may be associated and must be excluded. Drugs are another cause. Treatment with prednisolone is usually required.

The underlying causes of Sweet's disease are given in Fig. e43.3 and the systemic manifestations of Sweet's disease are given in Box e43.1.

Diagnostic criteria for Sweet's disease

- Major (2 needed)
  - Abrupt onset of typical lesions
  - Histology consistent with Sweet's
- Minor (2 needed)
  - Preceded by infection or vaccination, or in association with malignancy, inflammatory disorders or pregnancy
  - Presence of fever and constitutional symptoms and signs
  - Excellent response to prednisolone
  - 3 out of 4 of:
    - WBC >8
    - Neutrophils >70%
    - ESR >20
    - Raised CRP

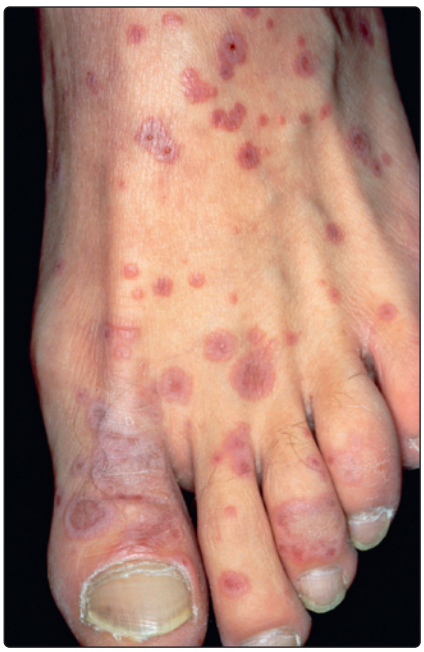


Fig. e43.1 Erythema multiforme showing classical erythematous plaques with dusky central skin, occasionally central necrosis/blistering. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Box e43.1 Systemic manifestations of Sweet's disease

- Common (>50%)
  - Fever, leukocytosis
- Less common (20–50%)
  - Arthralgia/arthritis/myalgia
  - Ocular involvement
- Uncommon
  - Neutrophilic alveolitis
  - Sterile osteomyelitis
  - Renal involvement (including mesangial glomerulonephritis, acute renal failure)
- Rare
  - Hepatitis
  - Myositis
  - Meningitis
  - Pancreatitis

(Adapted from Bolognia J, Jorizzo J, Schaffer J. 2012. Dermatology, 3rd edn. Mosby, Elsevier, London.)

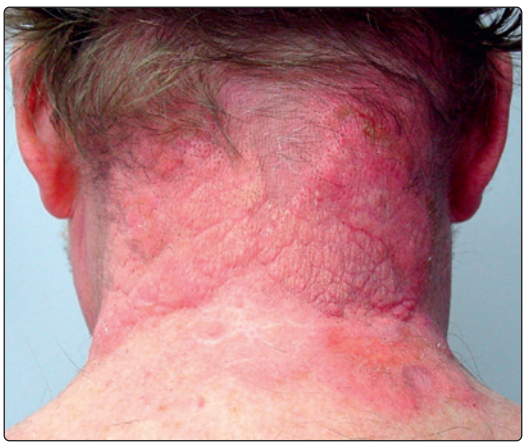


Fig. e43.2 Sweet's disease. Inflammatory exudative, eroded plaques can be seen on the posterior neck. *(From Callen JP, Jorizzo JL, Bolognia JL, Piette WW, Zone JJ 2003 Dermatological Signs of Internal Disease, 4th edition. Saunders, with permission.)*

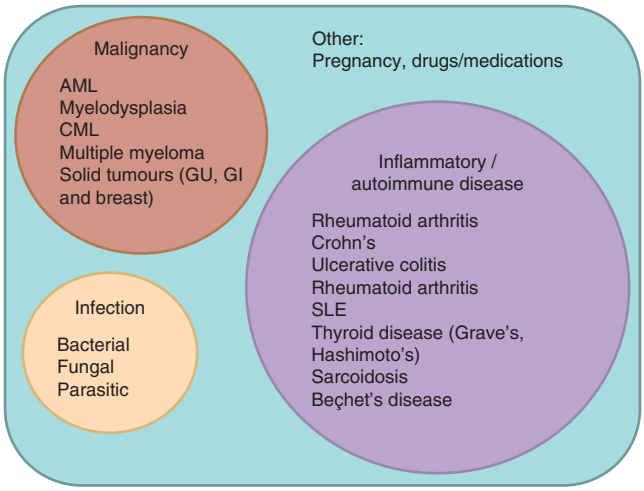


Fig. e43.3 Causes of Sweet's disease.

Treatment

Treatment with prednisolone 0.5–1 mg/kg per day is usually effective. It is important to treat any associated underlying disease. Other therapeutic options for persistent/resistant disease include indomethacin, doxycycline, colchicine, dapsone, methotrexate and ciclosporin. Recent use of biologic therapies has also been reported with adalimumab and infliximab.

GVH disease occurs when immunologically competent donor lymphocytes react against host tissues, principally the skin and gut. It is mostly associated with bone marrow transplantation, e.g. given for leukaemia or aplastic anaemia. Fever, malaise and a morbilliform eruption, which may progress to a condition similar to toxic epidermal necrosis, typify the acute GVH reaction. The acute type may be difficult to differentiate from a drug eruption, a viral infection or a cutaneous reaction to radiation therapy (Fig. e43.4). Chronic GVH disease may resemble lichen planus or systemic sclerosis. A skin biopsy often helps, and treatment with systemic steroids is usually needed.

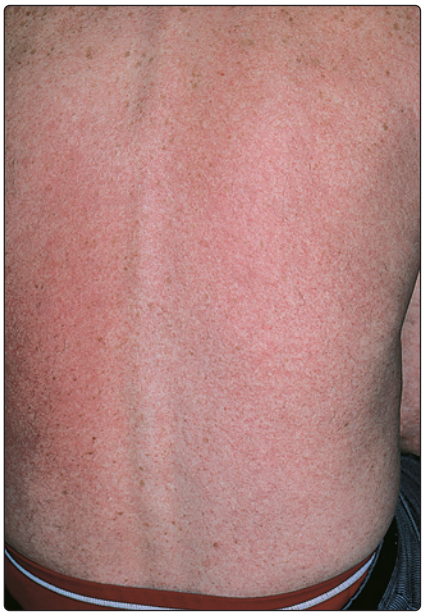


Fig. e43.4 Graft-versus-host disease. An acute eruption is shown in a patient following bone marrow transplant.

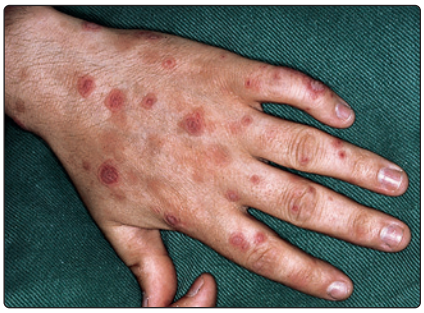


Fig. 43.2 Erythema multiforme. Target lesions are seen here on the dorsal aspect of the hand.

conjunctival and genital mucosae is not uncommon and, if extensive, is known as erythema multiforme major. Crops of new lesions appear for 2–3 weeks. The differential diagnosis includes drug induced exanthem (p. 90), Stevens–Johnson syndrome, toxic epidermal necrolysis, Sweet's disease, urticaria and pemphigoid. A biopsy is often helpful. *Toxic epidermal necrolysis* (p. 91) may sometimes represent erythema multiforme in a severe form.

Management

Identification and treatment of the underlying cause is the ideal. Mild cases resolve spontaneously and require symptomatic measures only. Extensive involvement necessitates hospital admission for supportive therapy. Systemic steroids are often prescribed to moderate the acute symptoms, although it is debatable whether they affect the outcome.

Erythema nodosum

Erythema nodosum is a panniculitis (i.e. an inflammation of the subcutaneous fat) that usually presents as painful red nodules on the lower legs. It is believed to result from CIC deposition in vessels of the subcutis. Infection, drugs and some systemic diseases are underlying causes (Table 43.3).

Clinical presentation

Deep, firm and tender reddish–blue nodules, 1–5 cm in diameter, develop on the calves (Fig. 43.3), shins and occasionally on the forearms. Joint pains and fever are common. Spontaneous resolution usually occurs within 8 weeks. Women are affected more than men (F:M ratio 3:1). Other causes of panniculitis (e.g. pancreatic disease, cold, trauma and lupus erythematosus), cellulitis and phlebitis need to be excluded. A skin biopsy is helpful. If tuberculosis or sarcoidosis is suspected, a chest radiograph and IGRA test (Ch. 26) are indicated.

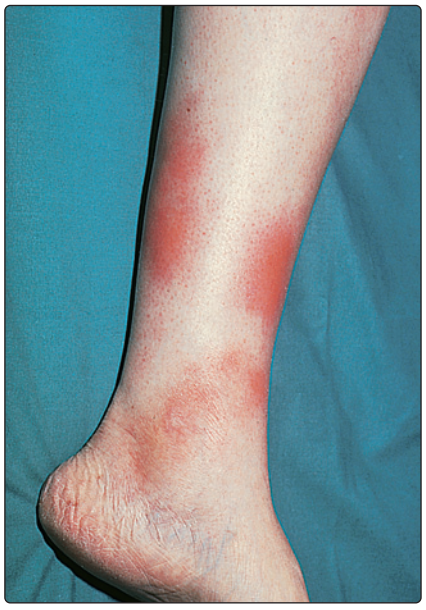


Fig. 43.3 Erythema nodosum of the lower leg.

Management

As spontaneous remission is usual, active therapy is rarely needed, although a non-steroidal antiinflammatory drug, potassium iodide or dapsone may help.

Sweet's disease

Sweet's disease (*acute febrile neutrophilic dermatosis*) occurs as raised plum-coloured plaques on the face or limbs (Fig. 43.4), typically with fever and a raised neutrophil count. It is not a true vasculitis but results from polymorph infiltration of the dermis.

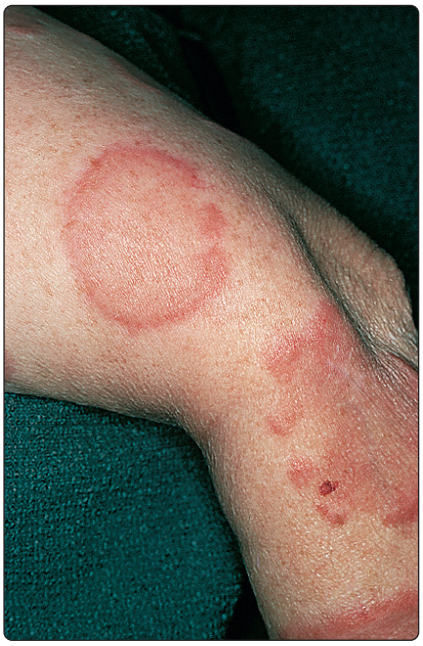


Fig. 43.4 Sweet's disease. A variant associated with rheumatoid arthritis is shown. Infiltrated annular plaques are seen on the arm.

Leukaemia, ulcerative colitis and other disorders may be associated and must be excluded. Drugs are another cause. Treatment with prednisolone is usually required.

Graft-versus-host (GVH) disease

GVH disease occurs when immunologically competent donor lymphocytes react against host tissues, principally the skin and gut. It is mostly associated with bone marrow transplantation, e.g. given for leukaemia or aplastic anaemia. Fever, malaise and a morbilliform eruption, which may progress to a condition similar to toxic epidermal necrosis, typify the acute GVH reaction. The acute type may be difficult to differentiate from a drug eruption, a viral infection or a cutaneous reaction to radiation therapy. Chronic GVH disease may resemble lichen planus or systemic sclerosis. A skin biopsy often helps, and treatment with systemic steroids is usually needed.

Table 43.3 **Causes of erythema nodosum**

Group	Cause
Idiopathic	About 20% of cases
Bacterial	Streptococci, TB, leprosy, *Yersinia*, *Mycoplasma*, *Salmonella*
Fungal	Coccidioidomycosis, *Trichophyton*
Viral	Cat-scratch fever, chlamydiae
Drugs	Sulphonamides, oral contraceptives
Systemic disease	Inflammatory bowel disease, sarcoidosis, Behçet's disease, malignancy (rare)

Vasculitis and the reactive erythemas

- **Vasculitis** is a circulating immune complex (CIC) disorder showing palpable purpura, sometimes with internal organ involvement. Investigations may reveal the underlying cause. Treatment with dapsone, prednisolone or other immunosuppressive drugs is often indicated.
- **Erythema multiforme** is an immune-mediated reaction with target and mucosal lesions, often due to infection, commonly herpes simplex, or drugs. The underlying cause should be sought.
- **Erythema nodosum** presents as painful red nodules on the lower legs and is regarded as a CIC response to infection (e.g. streptococcal), drugs or internal disease (e.g. sarcoidosis).
- **Sweet's disease** is characterized by plum-coloured plaques on the face and limbs. Leukaemia or a systemic disorder may be associated. A course of prednisolone is often required.

44 Skin changes in internal conditions

Skin signs are seen with many internal disorders and are not uncommonly their presenting feature. The astute dermatologist can recognize undiagnosed systemic disease. Skin changes are common in pregnancy (see Ch. 62). Sometimes itch alone is the primary symptom.

Skin signs of endocrine and metabolic disease

Almost all endocrine diseases (and several metabolic defects) have cutaneous signs that depend on the over- or underproduction of a hormone or metabolite (Table 44.1).

Diabetes mellitus

Candida albicans or bacterial infection is more common with untreated or poorly controlled diabetes. The neuropathy or arteriopathy of diabetes may result in *ulcers* on the feet (p. 76), and an associated secondary hyperlipidaemia can produce *eruptive xanthomas* (see Fig. 44.4). *Diabetic dermopathy* describes depressed pigmented scars on the shins, associated with diabetic microangiopathy. *Necrobiosis lipoidica* (Fig. 44.1), characterized by shiny atrophic yellowish–red plaques on the shins, was associated with diabetes in 65% of cases in one series, although others find a much lower figure. It affects less than 1% of all diabetics. Histologically, degenerate dermal collagen is seen with epithelioid cells and giant cells. The condition is chronic and may ulcerate. It is unresponsive to treatment. In contrast, *granuloma annulare* – recognized as palpable annular lesions on the hands, feet or face (Fig. 44.2) – is only rarely associated with diabetes and usually fades in 2 years. It must be differentiated from tinea corporis.

Table 44.1 **Skin signs of endocrine and metabolic disorders**

Disorders	Skin signs
Diabetes mellitus	Necrobiosis lipoidica, granuloma annulare, xanthomas, *Candida albicans* infection, 'dermopathy', neuropathic ulcers
Thyrotoxicosis	Pink soft skin, hyperhidrosis, alopecia, pigmentation, vitiligo, onycholysis, clubbing, pretibial myxoedema, palmar erythema
Myxoedema	Alopecia (including eyebrows), coarse hair, dry puffy yellowish skin (e.g. hands, face), asteatotic eczema, xanthomas
Addison's disease	Pigmentation (p. 78), vitiligo, loss of axillary and pubic hair
Cushing's disease	Pigmentation, hirsutism, striae, acne, obesity, buffalo 'hump'
Acromegaly	Thickened moist greasy skin, pigmentation, skin tags
Phenylketonuria	Fair hair and skin, atopic eczema (p. 38), photosensitivity
Hyperlipidaemia	Xanthomas (tuberous, tendinous, eruptive, plane), xanthelasma
Cutaneous porphyrias	Photosensitivity, blistering, skin fragility, atrophic scarring, thickening of skin, hypertrichosis, pigmentation (p. 48)

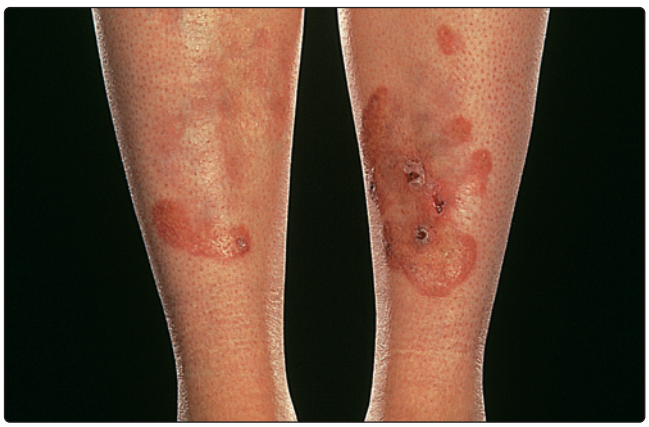


Fig. 44.1 Necrobiosis lipoidica. Yellowish–red atrophic areas are seen on the shins of a diabetic patient.

Thyroid disease

Both over- and underproduction of thyroxine result in skin and hair changes (see Table 44.1). *Pretibial myxoedema* (Fig. 44.3), seen in 1–10% of patients with hyperthyroidism, presents on the shins as raised erythematous plaques due to the deposition of mucin in the dermis. Topical steroids may be of benefit.

Flushing

Flushing may be physiological, drug/food induced or associated with *thyrotoxicosis*, but rarely with *carcinoid syndrome*, *mastocytosis* and *phaeochromocytoma*.

Hyperlipidaemia

Both primary (genetic metabolic defects) and secondary (associated with diabetes, hypothyroidism or the nephrotic syndrome) lipid abnormalities may produce a variety of xanthomatous deposits. These may be:

- *eruptive*: red–yellow papules on shoulders and buttocks (Fig. 44.4)
- *tendinous*: subcutaneous nodules; hand, foot or Achilles tendons
- *plane*: yellow–orange macules in palmar creases
- *tuberous*: yellow–orange nodules on knees and elbows.

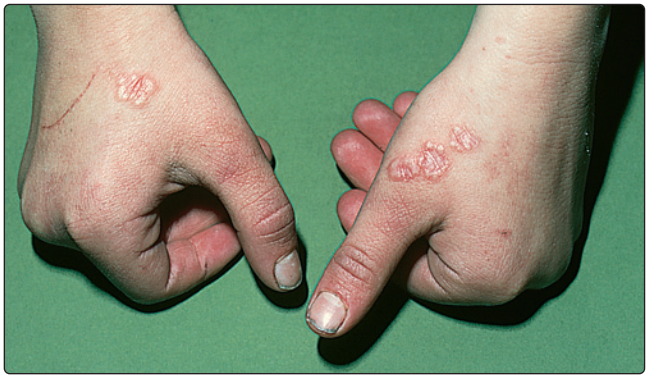


Fig. 44.2 Granuloma annulare, seen on the dorsal aspects of the hands.

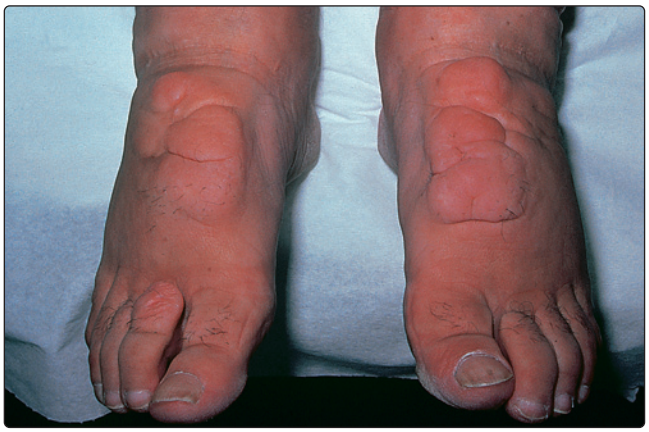


Fig. 44.3 Pretibial myxoedema. The patient had been thyrotoxic.

Itching or pruritus is an important symptom to elicit in any skin consultation. Sometimes, no primary skin disorder is evident and such cases may have an underlying disease. A list of appropriate investigations are suggested in Table e44.1.

Candida albicans or bacterial infection is more common with untreated or poorly controlled diabetes. The neuropathy or arteriopathy of diabetes may result in *ulcers* on the feet (p. 76), and an associated secondary hyperlipidaemia can produce *eruptive xanthomas* (see Fig. 44.4). *Diabetic dermopathy* describes depressed pigmented scars on the shins, associated with diabetic microangiopathy. *Necrobiosis lipoidica* (Fig. 44.1 and Fig. e44.1), characterized by shiny atrophic yellowish–red plaques on the shins, was associated with diabetes in 65% of cases in one series, although others find a much lower figure. It affects less than 1% of all diabetics. Histologically, degenerate dermal collagen is seen with epithelioid cells and giant cells. The condition is chronic and may ulcerate. It is unresponsive to treatment. In contrast, *granuloma annulare* – recognized as palpable annular lesions on the hands, feet or face (Fig. 44.2) – is only rarely associated with diabetes and usually fades in 2 years. It must be differentiated from tinea corporis.

Table e44.1 **Appropriate investigations for itching or pruritus**

Skin disease causing itching	Itch causing skin changes	Investigations
Eczema (any variant)	Uraemia	Renal function
Psoriasis	Obstructive biliary disease	Liver function
Urticaria	Lymphoma, leukaemia	Full blood count, ESR
Dermatophyte infections	Multiple myeloma	Immunoglobulins, serum electrophoresis
Lichen planus	Polycythaemia	Urine, Bence-Jones
Bullous pemphigoid	Iron deficiency	Iron/ferritin
Infestations (scabies)	Hyper or hypothyroidism	Thyroid function
Drug hypersensitivity	Opiate pruritus	Chest X-ray
Allergic contact dermatitis	Psychological	Others as indicated
Xerosis	Paraneoplastic	
	Senile pruritus	

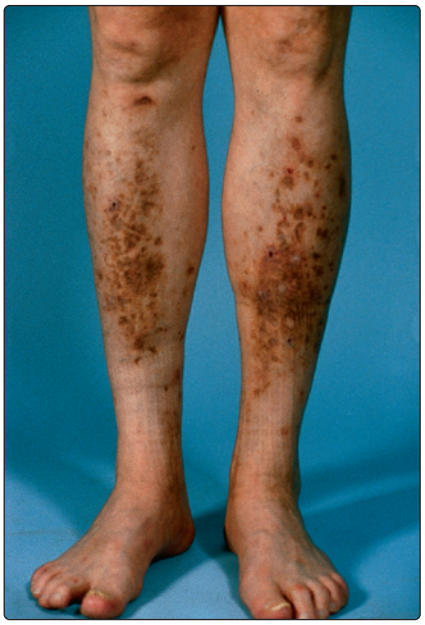


Fig. e44.1 Diabetic dermopathy. Note the brown macules and patches on the shins. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

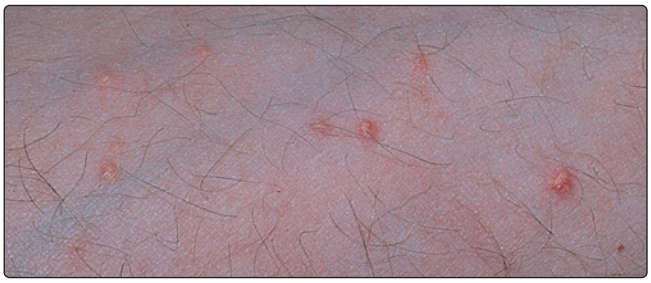


Fig. 44.4 Eruptive xanthomas. The patient had recently presented with diabetes mellitus.

Xanthelasma, seen as yellowish plaques on the eyelids, are not always due to a lipid abnormality. Treatment of xanthomas is usually aimed at underlying hyperlipidaemia.

Skin signs of nutritional and other internal disorders

Skin changes are common with nutritional deficiency and are not infrequent with gastrointestinal, hepatic and renal disease.

Nutritional deficiency

Protein malnutrition results in retarded growth, wasted muscles, oedema and skin changes of altered pigmentation, desquamation and ulcers with, in black Africans, dry and pale-brown/red hair. *Vitamin C deficiency* (scurvy) and *niacin deficiency* (pellagra) produce distinct lesions. In Europe, scurvy is mainly seen in elderly men who do not eat fresh fruit or vegetables. Deficiencies of other B vitamins and of iron also produce cutaneous changes (Table 44.2). *Acrodermatitis enteropathica* is a defect of zinc absorption, may be acquired or genetic, seen in weaned infants and cured by zinc supplements.

Gastrointestinal disease

Malabsorption and its deficiency states have accompanying skin problems that include dryness, eczema, ichthyosis, pigmentation and defects of the hair and nails. Some gut disorders show specific skin changes (see Table 44.2). *Coeliac disease* is associated with dermatitis herpetiformis (p. 83) and both *Crohn's disease* and *ulcerative colitis* induce various eruptions. *Peutz–Jeghers syndrome* (p. 79) and *pseudoxanthoma elasticum* (p. 97) affect both the skin and the gut. *Bowel bypass surgery* induces a vesiculopustular eruption.

Table 44.2 **Skin signs of nutritional and internal disorders**

Disorder	Skin signs
Protein malnutrition	Pigmentation, dry skin, oedema, pale-brown/orange hair
Iron deficiency	Alopecia, koilonychia, itching, angular cheilitis
Scurvy	Perifollicular purpura, bleeding gums, woody oedema
Pellagra	Light-exposed dermatitis and pigmentation
Acrodermatitis enteropathica	Perianal/perioral red scaly pustular eruption in infants, failure to thrive, diarrhoea, poor wound healing
Malabsorption	Dry itchy skin, ichthyosis, eczema, oedema
Liver disease	Pruritus, jaundice, spider naevi, palmar erythema, white nails, pigmentation, xanthomas, porphyria cutanea tarda, zinc deficiency, striae, gynaecomastia, lichen planus (p. 42)
Renal failure	Pruritus, pigmentation, white/red nails, dry skin with fine scaling
Pancreatic disease	Panniculitis, thrombophlebitis, glucagonoma syndrome
Crohn's disease	Perianal abscesses, sinuses, fistulae, erythema nodosum, Sweet's disease, necrotizing vasculitis, aphthous stomatitis, glossitis
Ulcerative colitis	Pyoderma gangrenosum, erythema nodosum, Sweet's disease
Sarcoidosis	Nodules, plaques, erythema nodosum, dactylitis, lupus pernio, scar granulomas, small papules, nail involvement

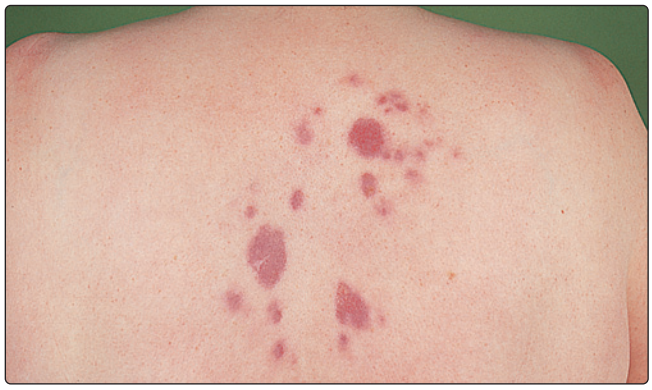


Fig. 44.5 Sarcoidosis. Plum-coloured plaques are seen on the upper back.

Other internal disorders

Hepatic and *renal disease*s often produce troublesome itching and pigmentation. Lesions may also be related to the underlying disease process, e.g. primary biliary cirrhosis (associated with systemic sclerosis) or vasculitis.

Sarcoidosis, a disorder of unknown aetiology in which granulomas commonly develop in the lung, lymph nodes, bone and nervous tissue, affects the skin in a third of cases. Cutaneous changes are variable and include brownish–red papules (typically on the face), nodules, plaques (on the limbs and shoulders, Fig. 44.5) and scar involvement. *Lupus pernio* is a particular pattern of sarcoidosis that appears as dusky-red infiltrated plaques on the nose or, occasionally, the fingers. *Erythema nodosum* may also result. Topical steroids have little effect. Resistant lesions may improve with intralesional steroid injection, but oral prednisolone or methotrexate is sometimes prescribed, particularly when there is progressive internal disease.

Calciphic uraemic arteriolopathy (syn. Calciphylaxis), usually associated with severe renal impairment, is an uncommon condition caused by intra and extra vascular calcium deposition in arteriole walls resulting in reduced flow and eventually occlusion. It presents as linear areas of cutaneous necrosis and ulceration often on the leg or abdominal folds. The condition is associated with increased calcium turnover, such as hyperparathyroidism, hyperphosphataemia and vitamin D supplementation in the uraemic associated variant of this condition, but calcium/phosphate levels are often normal. Non-uraemic variants may also be seen during treatment with warfarin and corticosteroids, as well as with liver dysfunction. Prognosis is poor and treatment is aimed at reducing calcium absorption. Treatment with intravenous sodium thiosulphate and unfractionated heparin may be beneficial.

Skin changes in internal conditions

- Endocrine and metabolic disorders, nutritional deficiencies and malabsorption are frequently associated with skin changes.
- Flushing may be physiological or induced by food, drugs or conditions such as thyrotoxicosis and carcinoid syndrome.
- Hyperlipidaemias are associated with a variety of xanthomata and xanthelasma, although the latter can occur with normal lipid levels.
- Liver and kidney failure, in particular, are complicated by pruritus and pigmentation. Treatment is often difficult.
- Inflammatory bowel disease and sarcoidosis have specific skin manifestations, often granulomatous or with cellular infiltration.
- Calciphic uraemic arteriolopathy is associated with severe renal impairment and is associated with severe cutaneous ulceration.

45 Drug eruptions

Reactions to drugs are common and often produce an eruption. Almost any drug can result in any reaction, although some patterns are more common with certain drugs. Not all reactions are 'allergic' in nature.

Aetiopathogenesis

Drug-induced skin reactions have several possible mechanisms:

- *Deposition* of the drug (or metabolites) in the skin, e.g. gold.
- *Excessive therapeutic effect*, e.g. bruising purpura with anticoagulants.
- *Immune hypersensitivity* (p. 10). HLA type can predict drug hypersensitivity reactions (Table 45.1).
- *Pharmacological side-effects*, e.g. bone marrow suppression by cytotoxics.
- *Unknown*, e.g. when drugs exacerbate psoriasis.

Clinical presentation

Drug eruptions present in many guises and come into the differential diagnosis of several rashes. It is vital to obtain a detailed drug ingestion history. This must include 'over-the-counter' preparations (e.g. for headaches or constipation) not normally regarded as 'drugs' by the patient. A drug introduced during a 2-week period before the eruption starts must be viewed as the most likely culprit, although a reaction may occur to a drug taken safely for years. The majority of drug eruptions fit into a defined category (Table 45.2). IgE mediated drug reactions are characterised by urticaria, angioedema and anaphylaxis – see Ch. 40.

Drug-induced exanthem

Drug-induced exanthem, the commonest type of drug eruption, may be *morbilliform* (measles-like) or *urticarial*, or may resemble *erythema multiforme*. It usually affects the trunk more than the extremities (Fig. 45.1), and may be accompanied by mild fever or followed by peeling of the skin. Haematological or biochemical disturbance does not arise. The eruption clears 1–2 weeks after stopping the offending drug.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

The rash is an exanthem of varying severity but typically has a delayed onset of 3–4 weeks. The individual is systemically unwell, characterized by fever and eosinophilia. Oedema of the head and neck is common, often with widespread lymphadenopathy. Occasionally, small pustules and vesicles may be evident. Liver dysfunction is frequent but any organ system can become involved and may fail. On cessation of the offending drug, the rash may improve only to worsen again days

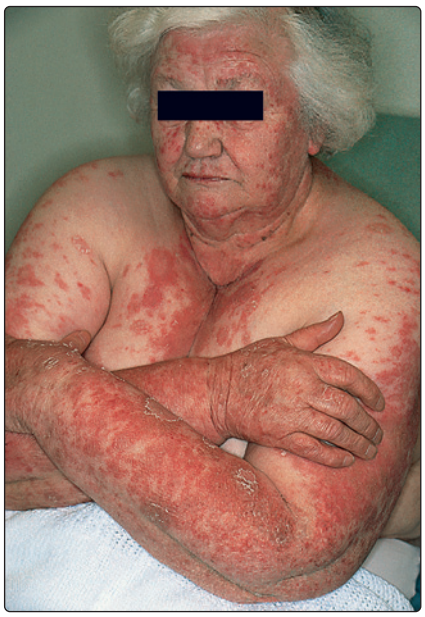


Fig. 45.1 Drug-induced exanthem. This morbilliform variant was due to chlorpropamide.

Table 45.1 **HLA associations of severe cutaneous drug eruptions**

Drug	HLA allele	Pattern
Abacavir[a]	B*5701	DRESS
Allopurinol	B*5801	SJS/TEN
Carbamazepine	A*3101	DRESS
Carbamazepine[a]	B*1502	SJS/TEN
Carbamazepine	B*1511	SJS/TEN
Dapsone	B*13:01	DRESS
Nevirapine	B*3505	DRESS

[a]HLA screening recommended prior to treatment (carbamazepine testing in those of Asian descent only).

Table 45.2 **Patterns of drug-induced skin disease**

Drug eruption	Description	Drugs commonly responsible
Acneiform	Like acne: papulopustules, no comedones	Androgens, bromides, dantrolene, isoniazid, lithium, phenobarbital, quinidine, steroids
Bullous	Various types; some phototoxic, some 'fixed'	Barbiturates (overdose), furosemide, nalidixic acid (phototoxic), penicillamine (pemphigus-like)
Drug-induced exanthem	Commonest pattern (see text)	Antibiotics (e.g. amoxicillin), proton pump inhibitors, gold, thiazides, allopurinol, carbamazepine
Eczematous	Not common; seen when topical sensitization is followed by systemic treatment	Neomycin, penicillin, sulphonamide, ethylenediamine (cross-reacts with aminophylline), benzocaine (cross-reacts with chlorpropamide), parabens, allopurinol
Erythema multiforme	Target lesions (p. 87)	Antibiotics, anticonvulsants, ACE inhibitors, calcium channel blockers, non-steroidals
Erythroderma	Exfoliative dermatitis (p. 46)	Allopurinol, captopril, carbamazepine, diltiazem, gold, isoniazid, omeprazole, phenytoin
Fixed drug eruption	Round red–purple plaques recur at same site	Antibiotics, tranquillizers, non-steroidals, phenolphthalein, paracetamol, quinine
Hair loss	Telogen effluvium (p. 70) Anagen effluvium	Anticoagulants, bezafibrate, carbimazole, oral contraceptive pill, propranolol, albendazole, cytotoxic drugs, acitretin
Hypertrichosis	Excess vellus hair growth (p. 71)	Minoxidil, ciclosporin, phenytoin, penicillamine, corticosteroids, androgens
Lupus erythematosus (LE)	LE-like syndrome (p. 84)	Hydralazine, isoniazid, penicillamine, anticonvulsants, beta-blockers, etanercept
Lichenoid	Like lichen planus (p. 42)	Chloroquine, beta-blockers, anti-TB drugs, penicillamine, diuretics, gold, captopril
Photosensitive	Sun-exposed sites, may blister or pigment (Fig. 45.4)	Non-steroidals, ACE inhibitors, amiodarone, thiazides, tetracyclines, phenothiazines
Pigmentation	Melanin or drug deposition (Fig. 45.5)	Amiodarone, bleomycin, psoralens, chlorpromazine, minocycline, antimalarials
Psoriasiform	Psoriasis flare	Beta-blockers, gold, methyldopa; lithium and antimalarials exacerbate psoriasis
Toxic epidermal necrolysis	Blistering skin with mucosal involvement (see text)	Antibiotics, anticonvulsants, non-steroidals, omeprazole, allopurinol, barbiturates
Urticaria	Many mechanisms (p. 80)	ACE inhibitors, penicillins, opiates, non-steroidals, X-ray contrast media, vaccines
Vasculitis	Immune complex reaction	Allopurinol, captopril, penicillins, phenytoin, sulphonamides, thiazides

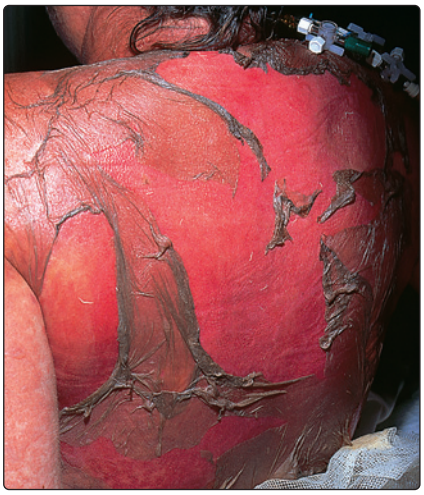


Fig. 45.2 Toxic epidermal necrolysis. The damaged epidermis has sheared off to leave extensive areas of eroded skin.

later leading to confusion regarding the diagnosis. This may be explained by viral reactivation (HHV6/7). Three to five days of oral prednisolone is usually effective. Autoimmune sequelae are recognized.

Stevens–Johnson syndrome, toxic epidermal necrolysis

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (Fig. 45.2) represent a spectrum of disease, characterized by severe mucosal ulceration and blistering of the skin with different body surface area detachment (SJS 1–10%; SJS/TEN overlap 10–30%; TEN>30%). Both show significant systemic disturbance. Mucosal lesions may lead to scarring with a significant morbidity if the patient survives. The extensive skin loss results in problems of fluid and electrolyte balance, as seen with extensive burns, and TEN must be managed in a burns or intensive care unit. Overall mortality is 30%.

Acute generalized exanthematous pustulosis (AGEP)

AGEP often arises rapidly after a new medication (<5 days). The condition is characterized by the presence of large sterile pustules, which may form sheets. The patient may have a mild systemic upset with a fever and usually has a neutrophilia. Pustular psoriasis can be difficult to distinguish.

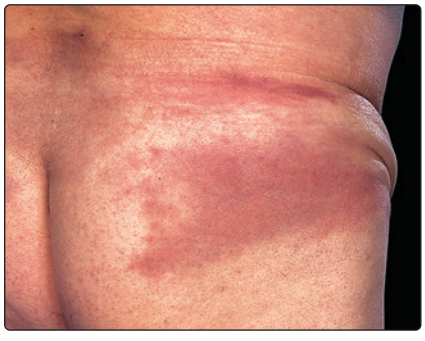


Fig. 45.3 Fixed drug eruption. The typical dusky erythematous lesion followed the ingestion of penicillin.

Fixed drug eruption

This specific but uncommon eruption is characterized by round red or purplish plaques (Fig. 45.3) that recur at the same site each time the causative agent is taken. The lesions may blister and leave pigmentation on clearing.

Fixed drug eruption, phototoxic reaction, drug-induced pemphigus and barbiturate overdosage (at pressure sites) may all blister (Table 45.2).

Differential diagnosis

The exact differential diagnosis depends on the type of drug eruption. The determination of which drug is responsible depends on a detailed prescribing timeline and a knowledge of the potential of each drug to cause a reaction (Table 45.3). In severe or extensive cases, photography and histology (including for direct immunofluorescence) should be obtained.

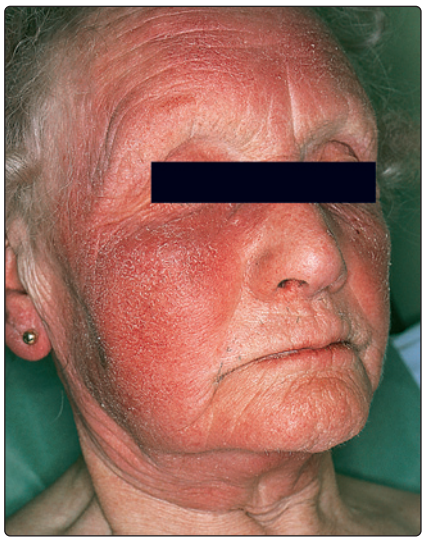


Fig. 45.4 Photosensitivity. This was caused by taking a thiazide diuretic, associated with being out of doors on a sunny day.

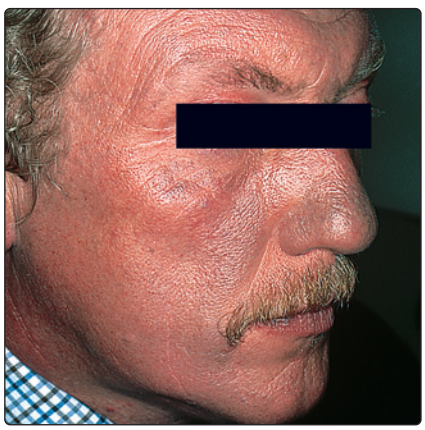


Fig. 45.5 Pigmentation. This was due to treatment with amiodarone for a cardiac arrhythmia. An erythematous eruption occurring within 2 h of sun exposure is more common.

Management

Withdrawal of the offending drug usually leads to clinical improvement in 2 days or so. Simple emollients or topical steroids can help to ease the eruption until it resolves. Patients should be given advice about which drugs they must avoid. For non-immediate reactions (i.e. not urticaria, angioedema, anaphylaxis-type) the *causative drug* can be identified by patch testing (best for drug exanthems and DRESS), intradermal testing (drug exanthems only), or challenge exposure (fixed drug eruption only). Allergen-specific IgE tests are generally not useful. New technologies include *in vitro* testing for drug induced T cell proliferation or cytokine production (p. 135.e1), and are completely safe, but these are not widely available.

Table 45.3 **Eruptions seen with some commonly prescribed drugs**

Drug	Eruption
ACE inhibitors	Pruritus, urticaria, toxic erythema
Antibiotics	Toxic erythema, urticaria, fixed drug eruption, erythema multiforme
Beta-blockers	Psoriasiform, Raynaud's phenomenon, lichenoid eruption
Non-steroidal antiinflammatories	Toxic erythema, erythroderma, toxic epidermal necrolysis
Oral contraceptives	Melasma, alopecia, acne, candidiasis
Phenothiazines	Photosensitivity, pigmentation
Thiazides	Toxic erythema, photosensitivity, lichenoid eruption, vasculitis

Drug eruptions

- Drug reactions may be pharmacological or idiosyncratic, as well as immune-mediated.
- Drugs that commonly cause drug eruptions are *amoxicillin*, *ACE inhibitors*, *anticonvulsants*, *thiazides* and *non-steroidal antiinflammatory drugs*.
- The commonest pattern is a *drug-induced exanthem*, often morbilliform.
- The most severe involvement is *toxic epidermal necrolysis*, which may be fatal.
- A drug eruption typically begins within 3 days of starting a drug (if it has been taken before) and clears about 2 weeks after stopping it.
- Withdrawal of the drug and avoidance of related compounds are necessary.
- Provocation tests are not recommended because of the possibility of a severe reaction.

Table e45.1 **SCORTEN assessment tool**

Clinical parameter	SCORTEN score	SCORTEN (out of 7)	Predicted mortality (%)
Age >40 years	Yes = 1	0–1	3.2
Malignancy	Yes = 1	2	12.1
Tachycardia >120/min	Yes = 1	3	35.3
Initial area of detachment >10%	Yes = 1	4	58.3
Serum urea >10 mmol/L	Yes = 1	≥5	90
Serum glucose >14 mmol/L	Yes = 1		
Bicarbonate <20 mmol/L	Yes = 1		

(From Bastuji-Garin et al. 1993. Arch Dermatol 129:92–96.)

Box e45.1 **Commonest causes SJS/TEN**

- Allopurinol
- Carbamazepine
- Lamotrigine
- Nevirapine
- Oxicam NSAIDs
- Phenobarbital
- Phenytoin
- Sulfamethoxazole and other sulfur antibiotics
- Sulfasalazine

The commonest causes of SJS/TEN are given in Box e45.1 and disease prognosis can be calculated from the SCORTEN assessment tool (Table e45.1).

Management of SJS/TEN

Management should be focused around:

A Making the correct diagnosis (skin biopsy for histology and immunofluorescence are mandatory)

B Immediate cessation of any potential culprit drugs

C General supportive measures
- analogous to burns
  - if skin detachment >10%, transfer to burns or intensive care unit
  - survival is proportional to the time taken to reach such units
- additional nutritional support
- analgesia
- warmed environments
- aseptic handling
- careful monitoring for systemic complications
- prevent complications of mucosal damage
  - involvement of ophthalmology and gynaecology
- Small areas of epidermal loss:
  - liquid and white soft paraffin ointment should be applied under low-adherent or soft polymer dressings
- Large areas of epidermal loss:
  - Biological dressings, epidermal allografts or xenografts have been used.

D Active treatments show unclear benefit but may include corticosteroids, intravenous immunoglobulin and ciclosporin.

E Aftercare
- Patient advice on causative agent and what to avoid
- Communication of suspected drug hypersensitivity with all clinicians involved in the patient's care.
- Reporting for pharmacovigilance
- Recognition and follow-up for chronic sequelae

46 Associations with malignancy

Internal malignancy causes a variety of skin changes (Table 46.1). Apart from direct infiltration, the mechanisms of these effects are often poorly understood. Some genetic conditions associated with malignancy include characteristic skin lesions that may arise before or after the cancer (e.g. mucosal lentigines in Peutz–Jeghers syndrome associated with bowel malignancy).

Conditions associated with malignancy

The following rare skin eruptions are characteristic and strongly indicate an underlying malignancy:

- acanthosis nigricans
- erythema gyratum repens
- necrolytic migratory erythema
- Paget's disease of the nipple
- extramammary Paget's disease
- skin secondaries.

Acanthosis nigricans

True acanthosis nigricans is uncommon. The flexures and neck typically show epidermal thickening and pigmentation (Fig. 46.1), and the skin is velvety or papillomatous. Warty lesions are seen around the mouth and on the palms and soles. *Benign acquired acanthosis nigricans* is more frequent and describes similar milder changes, seen with obesity or endocrine disorders such as insulin-resistant diabetes or acromegaly. Very rarely, acanthosis nigricans is *inherited* and appears in childhood or at puberty. In the malignancy-associated type, usually found in a middle-aged or elderly patient, the cancer is most commonly of the gastrointestinal tract. Growth factors, released from the tumour or associated with the endocrine disorder, cause the skin changes. The underlying disease must be identified and treated.

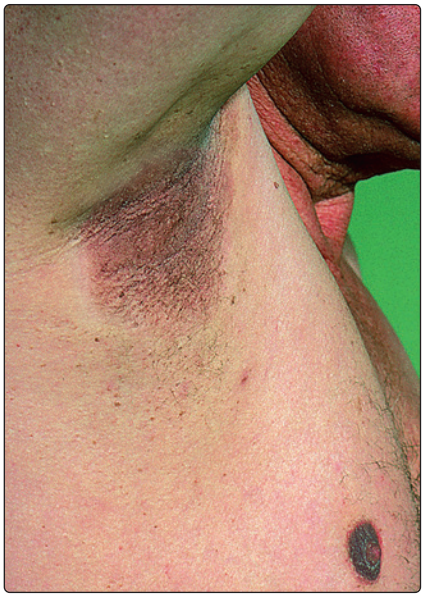


Fig. 46.1 Acanthosis nigricans. Pigmented velvety papillomatosis at the axilla and nipples is shown.

Erythema gyratum repens

Erythema gyratum repens is an exceptionally rare pattern of concentric scaly rings of erythema that shift visibly from day to day (Fig. 46.2). The appearance resembles wood grain. An underlying neoplasm, frequently a carcinoma of the lung, is almost invariably detected.

Necrolytic migratory erythema

Necrolytic migratory erythema is a rare paraneoplastic eruption of serpiginous erythematous plaques, with a migratory eroded edge. It typically starts in the perineum. The eruption indicates a tumour, or occasionally a hyperplasia, of the glucagon-secreting alpha cells of the pancreas (a *glucagonoma*). Weight loss, anaemia, mild diabetes, diarrhoea and glossitis are associated. Liver metastases are often present at diagnosis.

Paget's disease and extramammary Paget's disease

Paget's disease presents as a unilateral eczema-like plaque of the nipple areola and represents the intraepidermal spread of an intraductal breast carcinoma. Extramammary Paget's disease is seen as an eczema-like eruption around the perineum or axilla. It usually results from intraepidermal spread of a ductal apocrine carcinoma. A skin biopsy confirms the diagnosis prior to surgical excision.

Secondary deposits

Cutaneous metastases are not uncommon. They occur late, indicate a poor prognosis and may be the presenting sign of an internal tumour. Skin secondaries are multiple or solitary and appear as firm asymptomatic pink nodules (Fig. 46.3). The scalp, umbilicus and upper trunk are favoured sites. They occur most commonly with tumours of the breast, gastrointestinal tract, ovary and lung, and with malignant melanoma (p. 108). Leukaemias and lymphomas often show skin involvement (p. 110).

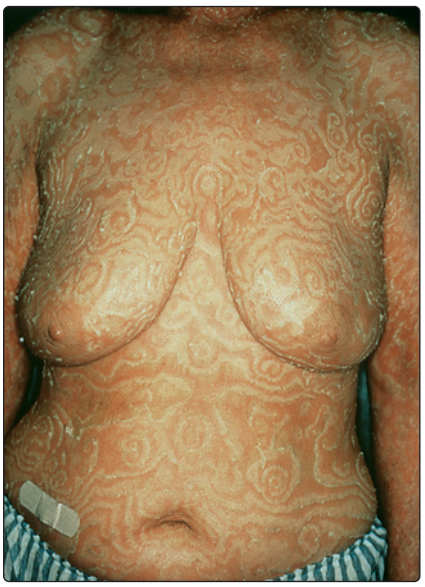


Fig. 46.2 Erythema gyratum repens. Note the 'wood grain' pattern.

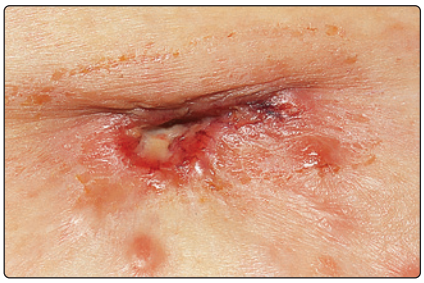


Fig. 46.3 Secondary deposit at the umbilicus from a carcinoma of the breast.

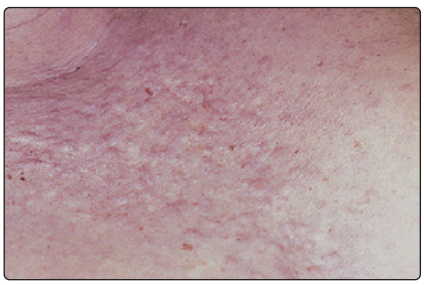


Fig. 46.4 Carcinoma en cuirasse. Direct pebbly infiltration of the skin of the chest wall from a carcinoma of the breast.

Direct infiltration of the skin causing sclerosis – carcinoma en cuirasse – is sometimes found with carcinoma of the breast (Fig. 46.4). Peau d'orange appearance and carcinoma erysipeloides (well demarcated red patch) and telangiectatic cutaneous metastases patterns are also recognized.

Conditions occasionally associated with malignancy

Conditions occasionally associated with underlying neoplasia but also seen with benign disease include:

The following rare skin eruptions are characteristic and strongly indicate an underlying malignancy (see also Table e46.1):

- acanthosis nigricans
- erythema gyratum repens
- necrolytic migratory erythema
- Paget's disease of the nipple
- extramammary Paget's disease
- skin secondaries.

Table e46.1 **Paraneoplastic dermatoses**

Dermatoses	Cutaneous findings	Comments
	Disorders that are associated with cancer in most or all cases	
Bazex syndrome (acrokeratosis paraneoplastica)	Acral psoriasiform plaques, typically with involvement of the nose and helices; often the lesions are violaceous. Longitudinal and horizontal ridging of the nails occurs in 75% of patients	By definition, this condition is linked to malignancy, generally occurring in the upper aerodigestive tract (pharynx, larynx or esophagus)
Carcinoid syndrome	Flushing and erythema of the head and neck. Pellagra-like dermatitis and sclerodermoid changes may develop in advanced disease	Flushing associated with ~10% of mid-gut tumors (small intestine, appendix, proximal colon) and liver metastases are required; type III gastric and bronchial carcinoid tumors are also associated with flushing (liver metastases are not required)
Erythema gyratum repens	Concentric erythematous lesions, often giving the appearance of grains of wood	Variable sites and types of malignancy
Acquired hypertrichosis lanuginosa (malignant down)	Growth of fine lanugo hairs in a generalized distribution in a generalized distribution or localized to the face. With time, these hairs may become coarser	Associated with a variety of internal malignancies, most often carcinoma of the lung, colon or breast
AESOP syndrome	Large red to violet-brown patch	Patch overlies a plasmacytoma
Ectopic adrenocorticotropic hormone (ACTH) syndrome	Generalized hyperpigmentation	Production of ACTH by a tumor (often a small cell carcinoma of the lung) may result in hyperpigmentation and features of Cushing's syndrome
Glucagonoma syndrome	Necrolytic migratory erythema, angular cheilitis, glossitis	Due to a glucagon-secreting tumor of the pancreas. Patients are often treated for intertrigo before the syndrome is diagnosed. Weight loss and diabetes mellitus accompany the dermatosis
Paraneoplastic pemphigus	Erosive disease of the mucous membranes and erythema multiforme-like, bullous pemphigoid-like or lichenoid skin lesions	Most often associated with non-Hodgkin lymphoma, chronic lymphocytic leukemia or Castleman's disease (with the latter accounting for the majority of cases in children and Asian populations). Castleman's tumors have been shown to produce the autoantibodies responsible for paraneoplastic pemphigus, and their resection can lead to remission of mucocutaneous lesions. Bronchiolitis obliterans is a common complication
POEMS syndrome (*polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes*)	Although the glomeruloid hemangioma is considered to be pathognomonic, it is present in a minority of patients. Other skin findings include cherry angiomas, hyperpigmentation, hypertrichosis, sclerodermatous thickening, hyperhidrosis, digital clubbing, plethora, acrocyanosis and leukonychia	Osteosclerotic myeloma, Castleman's disease and plasmacytomas have been reported in patients with POEMS. In addition to the findings designated in the acronym, patients may have peripheral edema, ascites, pulmonary effusions, papilledema, thrombocytosis, polycythemia and increased serum levels of VEGF
Sign of Leser-Trélat	Rapid appearance or growth of multiple seborrheic keratoses; keratoses may be inflamed	Often these patients have acanthosis nigricans and generalized pruritus. Controversy continues regarding the existence of this sign in the absence of generalized pruritus and acanthosis nigricans, in part because determining whether seborrheic keratoses are eruptive can be difficult. Eruptive seborrheic keratoses can also develop in erythrodermic patients who do not have an underlying malignancy
Tripe palms	Ridged velvety lesions on the palms	May or may not be accompanied by acanthosis nigricans
	Disorders that are strongly associated with cancer in a subset of cases	
Acanthosis nigricans	Rapid onset of hyperpigmented velvety changes of the flexural surfaces (e.g. neck, axillae and groin). May also involve extensor surfaces (e.g. elbows, knees and knuckles) and, in malignancy-associated cases, the lips, oral mucosa and palms (see above, tripe palms). Glossitis is also frequently present in malignancy-associated acanthosis nigricans	Association with adenocarcinoma of the stomach or other sites within the GI or GU tracts; in this setting, acanthosis nigricans is often accompanied by weight loss. Acanthosis nigricans is more commonly associated with endocrinologic abnormalities, particularly insulin resistance; such patients are typically overweight, and the onset of the condition is usually insidious
Anti-epiligrin cicatricial pemphigoid (AECP)*	Oral ulcerations, conjunctival erosions and scarring. Tense blisters and erosions of the skin may also develop	Roughly one-third of patients with AECP have or develop cancer within the first year following diagnosis. The cancer is usually an adenocarcinoma and is often at an advanced stage at the time of diagnosis, possibly accounting for the high mortality rate of AECP
Dermatomyositis (adult)*	Heliotrope, Gottron's papules, photodistributed poikiloderma, nailfold overgrowth with dilated capillary loops, pruritic diffuse scaly alopecia of the scalp.	Population-based studies demonstrate an overrepresentation of ovarian, lung, colorectal and pancreatic carcinomas and non-Hodgkin lymphoma in Caucasians

Continued

Table e46.1 **Paraneoplastic dermatoses—Continued**

Dermatoses	Cutaneous findings	Comments
Neutrophilic dermatoses	Sweet's syndrome or pyoderma gangrenosum (particularly the atypical bullous form)	Approximately 10–20% of cases are associated with hematologic disorders such as acute myelogenous leukemia or plasma cell dyscrasia (IgA). Underlying solid tumors are rare
Dermatoses that may be associated with cancer in a subset of patients		
Acquired angioedema due to C1 esterase inhibitor dysfunction	Acquired angioedema without associated wheals	Associated with B-cell lymphoproliferative disorders, including lymphomas, as well as monoclonal gammopathy of undetermined significance (MGUS)
Acquired ichthyosis	Resembles ichthyosis vulgaris; most often located on the legs	Lymphoma typically predates the diagnosis of the ichthyosis
Amyloidosis, primary systemic	Waxy, translucent or purpuric papules; periorbital and pinch purpura; macroglossia	Monoclonal gammopathy due to plasma cell dyscrasia ≫ multiple myeloma; deposits composed of immunoglobulin light chain (AL)
Cryoglobulinemia, type I	Retiform purpura and necrosis that favors cooler acral sites; acral cyanosis; livedo reticularis	Monoclonal gammopathy due to lymphoplasmocytic disorders
Cutaneous small vessel vasculitis	Palpable purpura	Less than 1% of patients with vasculitis have an associated malignancy, most commonly hairy cell leukemia and chronic lymphocytic leukemia
Dermatitis herpetiformis (DH)	Pruritic erosions and blisters on extensor surfaces, scalp and/or buttocks	Through the association of DH with gluten-sensitive enteropathy, enteropathy-associated T-cell lymphoma occasionally occurs
Exfoliative erythroderma	Diffuse, scaly, erythematous skin	May be associated with cutaneous T-cell lymphoma or, occasionally, with a systemic lymphoma or leukemia
Juvenile xanthogranulomas (JXGs) in the setting of neurofibromatosis 1 (NF1)	Pink-yellow to red-brown, dome-shaped papules and nodules, most often located on the head and neck	A triple association between JXGs, NF1 and JMML has been described
Multicentric reticulohistiocytosis	Nodular lesions, most often on the dorsal aspects of the hands.	A variety of associated malignancies have been reported, developing in approximately one-quarter of adult patients
Mycosis fungoides	Patch, plaque or nodular disease	Some studies have demonstrated an increased risk of second malignancies
Necrobiotic xanthogranuloma	Indurated xanthomatous plaques with necrosis and ulceration, usually in a periorbital location	Paraproteinemia (>80% of cases, most often IgG with κ light chains); multiple myeloma or a lymphoproliferative disorder develop in a minority of patients
Normolipemic plane xanthoma	Yellowish patches and thin plaques that favor the skin folds, upper trunk and periorbital area	Paraproteinemia, due to a plasma cell dyscrasia or lymphoproliferative disorder
Porphyria cutanea tarda (PCT)	Erosions, blisters and scars on the dorsal aspect of the hands, hyperpigmentation, hypertrichosis, milia	Through its association with hepatitis C virus, PCT may also be associated with primary hepatocellular carcinoma (hepatoma)
Schnitzler's syndrome	Chronic urticaria	Associated with an IgM κ paraproteinemia; lymphoplasmacytic malignancies develop in approximately 15% of patients. Additional manifestations include fevers, arthralgias and bone pain
Scleromyxedema	Sclerodermoid induration and a widespread eruption of firm, waxy papules arranged in linear arrays	Almost always associated with paraproteinemia (usually IgG with λ light chains); multiple myeloma develops in <10% of cases
Dermatoses that have been proven not to be associated with cancer		
Bowen's disease	Erythematous scaly plaque	The results of early studies that suggested an association with internal malignancy were likely explained by arsenic exposure in affected individuals and have not been replicated
Familial cancer syndromes and the skin		
• Cowden disease (breast, thyroid and GI carcinomas), Muir-Torre syndrome (GI carcinoma), Gardner syndrome (GI carcinoma), Peutz-Jeghers syndrome (various malignancies) • Costello syndrome (rhabdomyosarcoma, bladder carcinoma), Werner syndrome (sarcomas and other malignancies) • Birt-Hogg-Dubé syndrome, familial cutaneous leiomyomatosis (renal carcinoma) • Howel-Evans syndrome (esophageal carcinoma) • Ataxia-telangiectasia (leukemia, lymphoma, breast cancer) • Neurofibromatosis (malignant peripheral nerve sheath tumors, JMML, rhabdomyosarcoma, pheochromocytoma, carcinoid), tuberous sclerosis (renal carcinoma) • Multiple endocrine neoplasia syndromes • Dyskeratosis congenita (leukemia, Hodgkin disease) • Nevoid basal cell carcinoma syndrome (medulloblastoma, fibrosarcoma) • Bloom syndrome (lymphoproliferative and GI malignancies), Rothmund–Thomson syndrome (osteosarcoma), xeroderma pigmentosum (sarcomas, leukemia, GI and lung carcinomas) • Familial atypical mole and multiple melanoma syndrome (pancreatic carcinoma in a subset)		

*Statistical association

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Cutaneous metastases are not uncommon. They occur late, indicate a poor prognosis and may be the presenting sign of an internal tumour. Skin secondaries are multiple or solitary and appear as firm asymptomatic pink nodules (Fig. 46.3). The scalp, umbilicus and upper trunk are favoured sites. They occur most commonly with tumours of the breast, gastrointestinal tract, ovary and lung, and with malignant melanoma (p. 108). Leukaemias and lymphomas often show skin involvement (p. 110). Direct infiltration of the skin causing sclerosis – carcinoma en cuirasse – is sometimes found with carcinoma of the breast (Fig. 46.4 and Fig. e46.1). Peau d'orange appearance and carcinoma erysipeloides (well demarcated red patch) and telangiectatic cutaneous metastases patterns are also recognized.

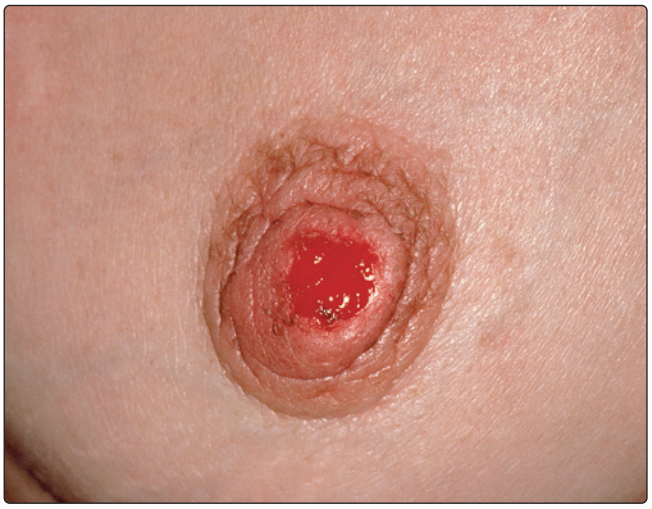


Fig. e46.1 Paget's disease of the breast. A chronic erythematous plaque surrounds the nipple. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

- acquired ichthyosis
- dermatomyositis (p. 85)
- erythroderma (p. 46)
- flushing (p. 74)
- generalized pruritus
- hyperpigmentation
- hypertrichosis (p. 71)
- pyoderma gangrenosum
- superficial thrombophlebitis
- tylosis (keratoderma; p. 94).

Acquired ichthyosis

Ichthyosis is usually inherited and starts in infancy (p. 94), but it may be acquired in adult life due to an underlying malignancy (e.g. Hodgkin's disease), essential fatty acid deficiency (e.g. caused by intestinal bypass malabsorption) or drug therapy with nicotinic acid, allopurinol and clofazimine.

Generalized pruritus

Generalized pruritus not associated with an eruption has several causes:

- idiopathic ('senile'), see page 122
- iron deficiency
- liver disease (cholestasis)
- malignancy, e.g. Hodgkin's disease
- neurological disorders
- polycythaemia
- renal failure (chronic)
- thyroid dysfunction.

Patients with generalized pruritus need careful examination and investigation to exclude liver disease (e.g. biliary obstruction), iron deficiency, polycythaemia, hypothyroidism, hyperthyroidism and renal failure. Pruritus may occur with multiple sclerosis and neurofibromatosis. Sometimes, especially in the elderly, no cause is found, and the itching is labelled *idiopathic*. The commonest malignant causes of pruritus are Hodgkin's disease (one-third of patients with this disease itch) and polycythaemia rubra vera. The aetiology of the itching is poorly understood. Treatment, once any underlying disorder has been dealt with, is symptomatic. Sedative antihistamines, calamine lotion and topical antipruritics (e.g. 0.5% menthol in aqueous cream) are used.

Table 46.1 **Cutaneous manifestations of malignancy**

Condition associated	Commonest malignancies
Almost always	
Acanthosis nigricans	Gastrointestinal tract
Erythema gyratum repens	Lung, breast
Extramammary Paget's disease	Apocrine glands
Necrolytic migratory erythema	Pancreas (alpha cells)
Paget's disease of the nipple	Breast
Skin secondaries	Breast, gastrointestinal, ovary, lung, kidney
Occasionally	
Acquired ichthyosis	Lymphoma (Hodgkin's disease)
Dermatomyositis	Lung, breast, stomach
Erythroderma	T cell lymphoma
Flushing	Carcinoid syndrome
Generalized pruritus	Hodgkin's disease, polycythaemia rubra vera
Hyperpigmentation	Cachectic malignancy
Hypertrichosis	Various tumours
Migratory thrombophlebitis	Pancreas, lung, stomach
Paraneoplastic pemphigus	B cell lymphoma, thymoma
Pyoderma gangrenosum	Leukaemia, myeloma
Tylosis	Oesophagus

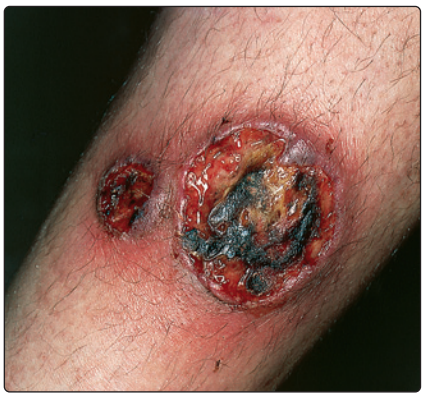


Fig. 46.5 Pyoderma gangrenosum. Necrotic ulcers shown on the lower leg.

Hyperpigmentation

Malignancy-associated pigmentation may result from ectopic adrenocorticotrophic hormone (ACTH) or melanocyte-stimulating hormone (MSH)-like hormone production by the tumour. It is also seen in patients with malignant cachexia. The axillae, groins and nipples are involved.

Pyoderma gangrenosum

Pyoderma gangrenosum starts as a pustule or inflamed nodule, which breaks down to produce an ulcer with an undermined purplish margin and a surrounding erythema (Fig. 46.5). The ulcer may extend rapidly. Lesions may be multiple. A bacterial gangrene (e.g. necrotizing fasciitis, p. 51) is sometimes misdiagnosed. Pyoderma gangrenosum often occurs on the trunk or lower limbs. An immune-mediated process is suggested. Malignancy and other diseases are associated:

- ulcerative colitis, Crohn's disease
- multiple myeloma and monoclonal gammopathy (often IgA)
- rheumatoid arthritis
- Behçet's syndrome (p. 127)
- chronic autoimmune liver disease
- leukaemia (a bullous form is seen).

Treatment is with systemic steroids, ciclosporin or anti-tumour necrosis factor (TNF) monoclonal antibodies. Topical tacrolimus helps mild disease. Cases associated with active inflammatory bowel disease can improve if this is treated.

Superficial thrombophlebitis

Migratory superficial thrombophlebitis, mainly associated with carcinoma of the pancreas or lung, also occurs with Behçet's syndrome.

Associations with malignancy

- **Acanthosis nigricans**, characterized by pigmentation and epidermal thickening of the flexures, neck, palms and soles, is seen with gastrointestinal cancers.
- **Benign acanthosis nigricans** is more common and occurs with obesity or endocrine disorders.
- **Erythema gyratum repens** is a migratory erythema almost invariably associated with a neoplasm.
- **Paget's disease**, an eczema-like plaque at the nipple, is due to epidermal spread of an intraductal carcinoma. The *extramammary* form comes from an apocrine carcinoma.
- **Secondary deposits** are not uncommon and may present as single or multiple pink firm nodules, often on the scalp or upper trunk. They occur with tumours of the breast, gastrointestinal tract, ovary and lung and with malignant melanoma.
- **Acquired ichthyosis** is associated with Hodgkin's disease, fatty acid deficiency (e.g. intestinal bypass malabsorption) and as a side-effect of some drugs.
- **Generalized pruritus** may occur with malignancy (e.g. Hodgkin's disease), liver disease, renal failure, iron deficiency and thyroid dysfunction.
- **Pyoderma gangrenosum** is a necrotic ulceration seen with ulcerative colitis, Crohn's disease, rheumatoid arthritis, multiple myeloma or leukaemia.

47 Keratinization and blistering syndromes

Common skin disorders, e.g. atopic eczema or psoriasis, have a genetic component that is often subject to environmental influences. The *genodermatoses* differ in being single gene defects and include keratinization, blistering and neurocutaneous syndromes.

The ichthyoses

The ichthyoses are inherited disorders of keratinization and epidermal differentiation. They are characterized by dry scaly skin and vary from mild and asymptomatic to severe and incompatible with life (Table 47.1). Keratinization is abnormal. Some of the biochemical defects have been identified, e.g. steroid sulphatase is deficient in X-linked ichthyosis.

Clinical presentation

Ichthyosis vulgaris (homozygous mutation in *FLG*) is common and unrecognized if mild. Small bran-like scales are seen on the extensor aspects of the limbs and the back (Fig. 47.1). The flexures are often spared.

The other types of ichthyosis are uncommon or rare and can usually be identified by their clinical features, onset and inheritance. Autosomal dominant conditions tend to improve with age, whereas recessive ichthyoses may worsen. *Collodion baby* describes a newborn infant with a tight shiny skin that causes feeding problems and ectropion. It is mainly due to non-bullous ichthyosiform erythroderma. *Acquired ichthyosis* (p. 93) usually starts in adulthood.

Table 47.1 **A classification of the ichthyoses**

Disorder	Inheritance	Clinical features
Ichthyosis vulgaris	Autosomal dominant	Common (1 in 250). Onset 1–4 years. It occurs with atopic eczema. Often mild. Small bran-like scale seen. Flexures spared. Defect in filaggrin, needed for keratin assembly
X-linked ichthyosis	X-linked recessive	1 in 2000 males. Generalized involvement with large brown scale. Onset in first week of life. Improves in summer. Due to a deficiency of steroid sulphatase
Non-bullous ichthyosiform erythroderma[a]	Autosomal recessive	Rare (1 in 300,000). At birth may present as collodion baby. Red scaly skin and ectropion may follow. Erythema improves with age
Bullous ichthyosiform erythroderma[b]	Autosomal dominant	Rare (<1 in 100,000). Redness and blisters occur after birth but fade. Warty rippled hyperkeratosis appears in childhood

[a]Lamellar ichthyosis is similar but rarer.
[b]Also called 'epidermolytic hyperkeratosis'.

Management

Emollient ointments, creams and bath additives (p. 22) are essential and adequate for mild ichthyosis. Urea-containing creams (e.g. Aquadrate or Calmurid) help, but severe forms may need oral acitretin (p. 31).

Keratoderma

Keratoderma describes gross hyperkeratosis of the palms and soles, and may be acquired or inherited.

Clinical presentation

The degrees of involvement and modes of inheritance vary. A common pattern, *tylosis*, shows diffuse hyperkeratosis of the palms and soles (Fig. 47.2) and is usually of autosomal dominant inheritance. In a few families, tylosis is associated with carcinoma of the oesophagus. Other keratodermas may give punctate papular lesions on the palms and soles or, in 'mutilating' types, fibrous bands that strangulate digits.

Acquired palmoplantar keratoderma is seen in pityriasis rubra pilaris (p. 46) and lichen planus, and may develop in women at menopause, particularly around the heels. Corns and callosities are different from keratoderma. *Callosities* are painless localized thickenings of the keratin layer and are seen as a protective response, induced by friction or pressure, which is often occupational in origin. *Corns* are painful and develop at areas of high local pressure on the feet, where shoes squeeze against bony points.

Management

Treatment is with keratolytics, e.g. 5–10% salicylic acid ointment or 10% urea cream. Topical calcipotriol can be helpful. Sometimes the use of oral acitretin or alitretinoin is justified.

Keratosis pilaris

Keratosis pilaris is a common, sometimes inherited condition, in which multiple small horny follicular plugs affect the upper thigh, upper arm and face (Fig. 47.3). It is occasionally associated with ichthyosis vulgaris. Application of 5% salicylic acid ointment or 10% urea cream lessens, but does not cure, the problem.

Darier's disease

Darier's disease (keratosis follicularis) is a rare autosomal dominant condition

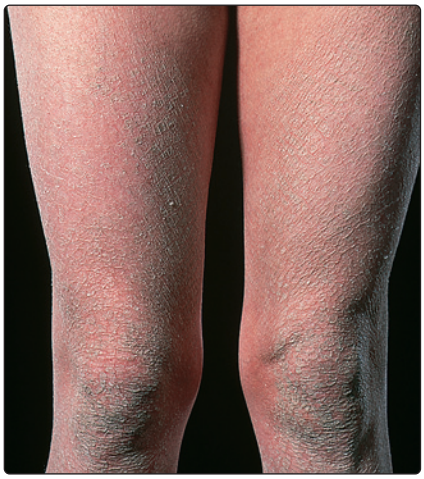


Fig. 47.1 Ichthyosis vulgaris showing bran-like scaling.

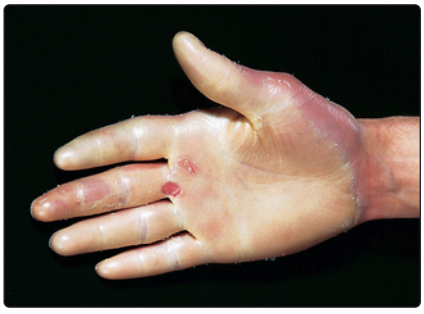


Fig. 47.2 Keratoderma of the palm.

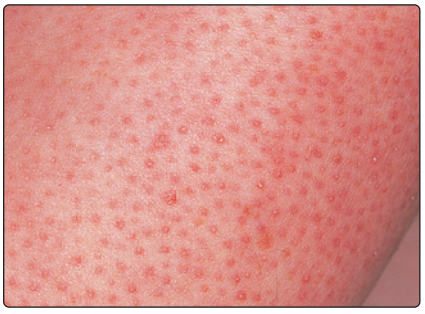


Fig. 47.3 Keratosis pilaris on the upper arm.

In *ichthyosis vulgaris* expression of epidermal filaggrin is defective, leading to the clinical picture of white or grey, small bran-like, dry semi-adherent scales. The same filaggrin mutation also predisposes to atopic disease (eczema and asthma), seen in one-third to one-half of patients with ichthyosis vulgaris (there may be difficulty in distinguishing the xerosis of atopic eczema from the dry scales of ichthyosis).

In *ichthyosis vulgaris*, the ichthyotic changes are most prominent on the extensor aspects of the limbs. The flexures are characteristically spared (as may be the palms and soles), the abdomen may be mildly affected, and the face often shows involvement. The signs and symptoms show a seasonality, with improvement in warm sunny weather. About one-third of individuals show improvement in adolescence.

Typically in *X-linked recessive ichthyosis*, an affected male has inherited, from his asymptomatic carrier mother, an X chromosome bearing the mutated steroid sulphatase gene. In most cases, light flaky scaling is evident in the first week of life. Scaling increases during childhood, spreading up from the lower legs to the trunk, and may stabilize in the teens with little subsequent fluctuation (apart from improvement in summer), although there is variability in severity (Fig. e47.1a). Systemic features include corneal opacities and testicular anomalies.

Lamellar ichthyosis is a rare autosomal recessive disease that typically presents at birth as a collodion baby. The collodion membrane is gradually replaced by generalized large scales (Fig. e47.1b).

Molecular diagnosis in the ichthyoses is through a variety of molecular techniques from a blood sample or hair root sample (or fresh skin biopsy).

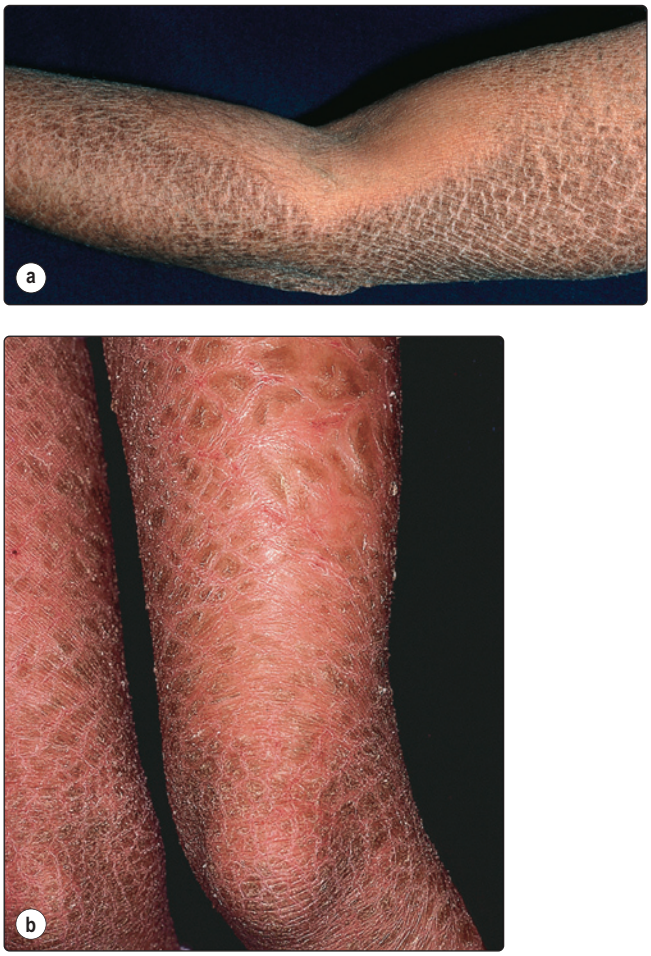


Fig. e47.1 Ichthyosis (a) X-linked ichthyosis. Large scales are evident on the arm and forearm. In this instance, there is sparing of the antecubital fossa but this is not invariable. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)* **(b) Lamellar ichthyosis.** Large plate-like scales are evident in a mosaic pattern on the legs. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

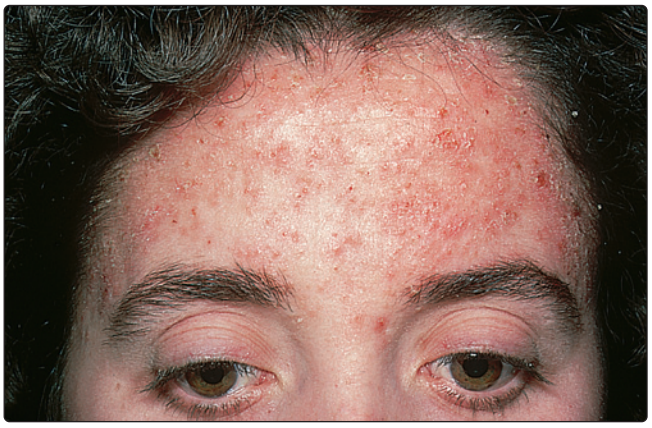


Fig. 47.4 Darier's disease affecting the forehead.

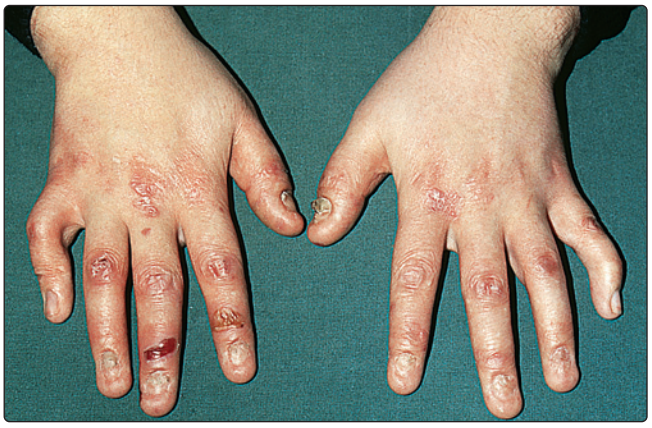


Fig. 47.5 Epidermolysis bullosa. The dystrophic dominant type is shown.

characterized by brownish scaly papules. The abnormal gene is sited on chromosome 12q and encodes calcium adenosine triphosphatase.

Keratinocyte tonofilaments and desmosomes are dissociated on electron microscopy.

Clinical presentation

The disease presents in teenagers or young adults, with small brown, greasy scaled papules, typically on the flexures, upper back, chest and forehead (Fig. 47.4). Its onset may follow sunburn. The severity varies from being mild and almost unnoticed to being extensive and severe. Nail changes (p. 72) and palmar pits or keratoses are found. Bacterial infection or eczema herpeticum (p. 39) may occur.

Management

Mild Darier's disease requires topical emollients and advice on sun avoidance. Topical retinoids, e.g. tretinoin or adapalene, may help. More severe cases are greatly helped by oral acitretin (p. 31).

Flegel's disease

Flegel's disease (hyperkeratosis lenticularis perstans) is a rare, dominantly inherited disorder, characterized by keratotic plugs on the legs and arms. It starts in middle age. When larger plugs are seen, it is called *Kyrle's disease*, but the two types may coexist.

Epidermolysis bullosa

Epidermolysis bullosa (EB) defines a group of genetically inherited diseases characterized by skin fragility and blistering on minimal trauma. They range from being mild and trivial to being incompatible with life (Table 47.2).

Table 47.2 **The main types of epidermolysis bullosa (EB)**

Disease	Inheritance	Clinical features
Simple EB	Autosomal dominant	Commonest type. Often mild and limited to hands and feet. Blisters caused by friction. Nails and mouth unaffected
Junctional EB	Autosomal recessive	Rare and often lethal. At birth, large erosions seen around mouth and anus. Slow to heal. No effective treatment
Dystrophic EB	Autosomal dominant	Hands, knees and elbows are affected. Scarring with milia is found. Deformity of the nails may occur
Dystrophic EB	Autosomal recessive	Starts in infancy. Severe blistering results in fusion of fingers and toes, with mucosal lesions and oesophageal stricture

Aetiopathogenesis

Keratin synthesis is defective in simple EB (genes mapped to chromosomes 12 and 17). Collagen VII is abnormal in dystrophic EB (gene sited on chromosome 3). Anchoring fibrils (p. 3) are defective in certain types of EB.

Clinical presentation and management

Simple EB is fairly common and requires avoidance of trauma. The more severe forms (Table 47.2 and Fig. 47.5) need to be managed in specialized centres. Avoidance of trauma, supportive measures and the control of infection are important. Treatment with various drugs has given disappointing results. *Acquired EB*, with an onset in adult life, shows trauma-induced blistering and resembles pemphigoid on immunofluorescent studies.

Prenatal diagnosis of inherited disorders

DNA-based prenatal diagnosis is now possible for junctional and recessive dystrophic EB, bullous ichthyosiform erythroderma and oculocutaneous albinism. DNA is obtained in the first trimester from chorionic villus samples or amniotic cells. Mid-second trimester fetal skin biopsy is still used for diseases where the gene is unknown but biopsy changes are specific.

Inherited keratinization and blistering disorders

- **The ichthyoses** are inherited disorders of keratinization. The skin is dry and scaly. Emollient therapy is helpful. Certain ichthyoses may present at birth as a collodion baby.
- **Darier's disease** is a rare autosomal dominant condition. Greasy scaly papules are seen on the chest, back and in the flexures. Severe cases are treated with acitretin.
- **Keratoderma** is typified by hyperkeratosis of the palms and soles and is treated by keratolytics. Oral acitretin is sometimes required.
- **Keratosis pilaris** is a common condition in which horny follicular plugs are seen on the limbs and face. Treatment is difficult; emollients may help.
- **Flegel's disease** is a rare dominantly inherited disorder characterized by keratotic plugs on the legs and arms. Larger plugs suggest *Kyrle's disease*.
- **Epidermolysis bullosa** describes inherited bullous diseases ranging from mild blistering induced by ill-fitting shoes to severe and lethal blistering present at birth.
- **Prenatal diagnosis** of several rare, severe, inherited skin diseases is now possible using DNA technology.

Histologically, Darier's disease is characterized by dyskeratotic keratinocytes which separate from their epidermal neighbours.

Darier's disease has a prevalence of about 1 in 35,000 in Britain. Many different mutations of the calcium ATPase gene have been identified.

Clinically, the 'seborrhoeic' areas of the chest, back, face and scalp are most involved, although the limbs may be affected (Fig. e47.2). Flexural involvement may become secondarily infected and is difficult to treat.

Localized EB simplex is characterized by blisters on the feet (occasionally elsewhere) brought on by friction from footwear, especially in hot weather. Symptoms typically have their onset in childhood. *Other forms of EB* are rare but often very serious when they do occur. As regards treatment for the severe forms of EB, there is the potential for gene therapy, though this has not yet become a reality.

Patient self-help organizations

Although the genodermatoses manifest in a wide spectrum of clinical phenotypes, coping with a life-long disease is often difficult for the patient and for the parents, such that psychological support as well as practical advice are frequently needed. The patient support groups are a very useful resource in this situation. The Ichthyosis Support Group (http://www.ichthyosis.org.uk/) and the Foundation for Ichthyosis and Related Skin Types ('FIRST' http://www.firstskinfoundation.org/) help sufferers with ichthyosis, and the Darier's Disease Support Group (http://www.mdjunction.com/dariers-disease) provides an online forum for those affected by Darier's disease ('FIRST' also supports Darier's disease). DEBRA (the Dystrophic Epidermolysis Bullosa Research Association: http://www.debra.org.uk/) is a large charity that provides all levels of support to patients and to dermatologists including the facility of skilled nurses who can become involved to help with the initial diagnosis (by performing skin biopsies) and management if the disease is suspected in a newborn (in the United States, the organization is DEBRA of America: http://www.debra.org/).

Further reading – online sources

More detailed information on the genodermatoses is available at the website of the National Centre for Biotechnology Information (access via http://www.ncbi.nlm.nih.gov/). The Genetic Home Reference website (access via http://ghr.nlm.nih.gov/condition/) and the DEBRA website (access via http://www.debra.org.uk) give more detailed information on other types of EB and details of techniques for prenatal diagnosis.

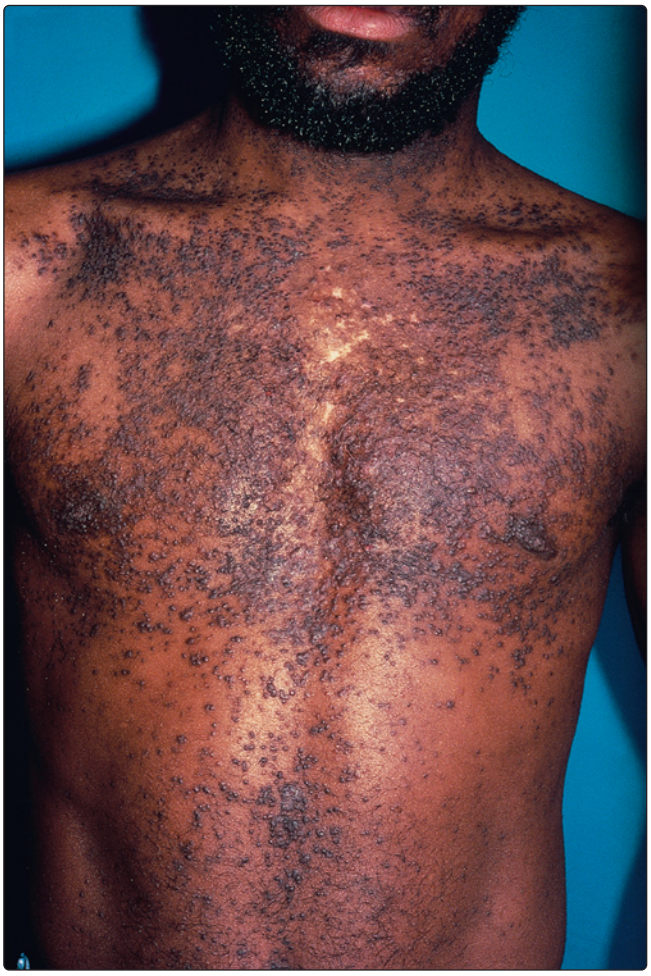


Fig. e47.2 Darier's disease affecting the trunk. Coalescing warty papules are present. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Further reading – textbooks

Spritz, J.L., 2005. Genodermatoses, second ed. Lippincott Williams & Wilkins, Philadelphia, PA.

Tadini, G., Brena, M., Gelmetti, C., Pezzani, L., 2015. Atlas of Genodermatoses, second ed. CRC Press, Boca Raton, FL.

48 Neurocutaneous disorders and other syndromes

Certain inherited skin disorders also have significant involvement of internal organs. The neurocutaneous disorders, the inherited diseases of connective tissue and the premature ageing syndromes are included.

Neurofibromatosis

von Recklinghausen's neurofibromatosis (NF1) is relatively common, affecting about 1 in 3000 births. Café-au-lait spots, cutaneous neurofibromas and other bony or neurological abnormalities characterize NF1. The disease shows autosomal dominant inheritance, although 50% of cases are new mutations.

Aetiopathogenesis

The *NF1* gene is a tumour suppressor gene, mapped to chromosome 1. Prenatal screening for the NF1 gene is available by amniocentesis or chorionic villus biopsy.

Clinical presentation

The two main cutaneous features are:

1. *Café-au-lait spots*: round or oval coffee-coloured macules, due to increased melanin pigment. They often appear in the first year of life. One or two café-au-lait spots are seen in 10% of normal people but, in neurofibromatosis, six or more are usually present. Freckling of the axilla is also found (Fig. 48.1).
2. *Dermal neurofibromas*: small nodules that appear during childhood and increase in number at the time of puberty (Fig. 48.2). Their number varies from a few to several hundred.

A proportion of patients with NF1 have short stature and macrocephaly. Rare variants of the disease are occasionally seen. The commonest is NF2 (*central neurofibromatosis*), in which patients have bilateral acoustic neuromas but few, if any, café-au-lait spots or dermal nodules. NF2 also shows autosomal dominant inheritance. The *NF2* gene is on chromosome 22.

Complications

Complications develop in many cases and include the following:

- *Plexiform neurofibromas* are larger than their dermal counterparts and measure up to several centimetres in size. They are associated with pigmentation and hypertrophy of the overlying skin or underlying bone, and present a cosmetic problem.
- *Benign tumours of the nervous system* may develop. These include optic gliomas, acoustic neuromas and spinal neurofibromas that arise from nerve roots of the spinal cord.
- *Sarcomatous change* in a neurofibroma, typically non-cutaneous, occurs in 1.5–15% of cases.
- *Kyphoscoliosis* (in 2%) or bowing of the tibia and fibula may occur.
- *Other problems* include iris hamartomas (Lisch nodules), hypertension, epilepsy and learning difficulties.

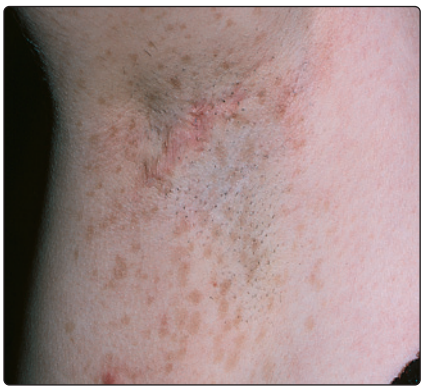


Fig. 48.1 Neurofibromatosis showing axillary freckling.

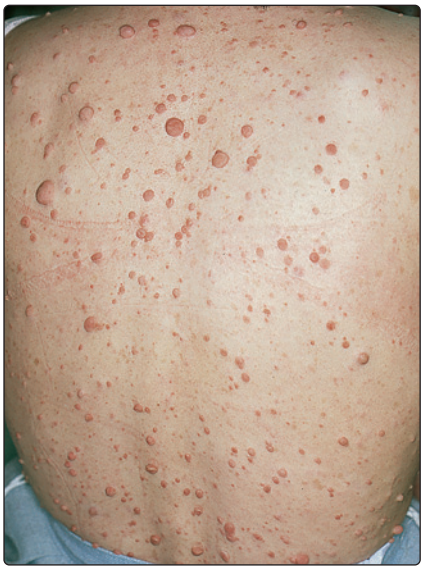


Fig. 48.2 Neurofibromatosis. Multiple neurofibromas are present on the back.

Management

Once the diagnosis has been made, genetic counselling and the exclusion of any complicating factors are important. Troublesome nodules can be excised, and larger disfiguring neurofibromas removed by plastic surgery. Patients are often helped by contact with a patient support group.

Tuberous sclerosis complex

Tuberous sclerosis complex is an autosomal dominant condition of variable expression with an incidence of 1 in 10,000. About 60–70% of patients have new mutations. Complex hamartomas occur in several organs. The abnormal genes have been mapped to chromosomes 9 and 16.

Clinical manifestations

The features may not appear until puberty. Patients typically show the following:

- *Adenoma sebaceum*: red–brown angiofibromatous papules that are usually found around the nose (Fig. 48.3). They appear in childhood.
- *Periungual fibromas*: pink fibrous projections are seen under the nail folds (Fig. 48.4).

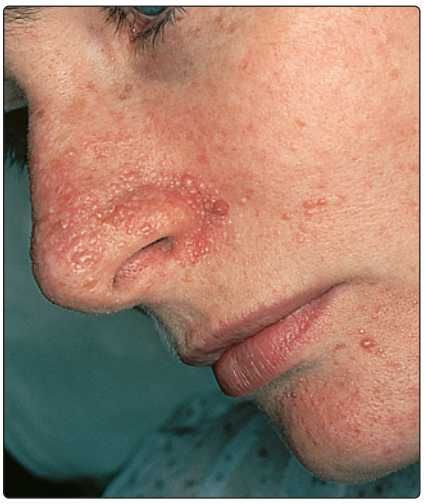


Fig. 48.3 Tuberous sclerosis. Angiofibromas are seen at the sides of the nose.

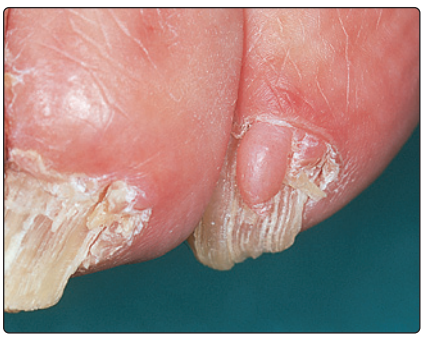


Fig. 48.4 Tuberous sclerosis showing periungual fibromas.

Neurofibromatoses and tuberous sclerosis, along with Sturge–Weber syndrome and von Hippel–Lindau disease, are among conditions known as the 'RASopathies'. In these disorders, there are germline mutations in genes affecting the RAS subfamily of proteins and mitogen-activated protein kinases, which control signal transduction within cells.

Widespread genetic testing for the NF1 gene so far has been hampered by the large size of the gene (335 kb, with at least 59 exons).

At presentation, a detailed clinical examination is needed together with a variety of neurophysiological, audiological, radiological and ocular investigations. These are best done by someone who has expertise in managing the condition.

Course of the disease

The clinical course of patients with NF1 neurofibromatosis is very variable. Most patients with the syndrome will have a benign course. Early onset and rapid progression of lesions during puberty usually indicate a poor prognosis.

Differential diagnosis and genetic counselling

Recently, a condition called *Legius syndrome*, characterized by café-au-lait macules but lacking Lisch nodules or neurofibromas, was described. This needs to be distinguished from NF1. At present, the treatment of NF1 is symptomatic. Genetic counselling is important.

Tuberous sclerosis complex is an autosomal dominant condition of variable expression with an incidence of 1 in 10,000. About 60–70% of patients have new mutations. Complex hamartomas occur in several organs principally the skin, brain, eye, kidney and heart. The abnormal genes have been mapped to chromosomes 9 and 16.

- *Shagreen patches*: connective tissue naevi, soft, yellowish with a cobblestone surface, are found on the lumbosacral region.
- *Ash-leaf macules*: small (1–3 cm long) white oval macules, sometimes present at birth, and best seen with a Wood's light.
- *Neurological involvement*: learning difficulties and epilepsy affect 60–70% of cases. Intracranial calcification is seen.
- *Other features*: retinal phacomas, cardiac rhabdomyomas and renal tumours are found.

Management

An affected individual should have a full clinical examination, often with radiographs and magnetic resonance imaging (MRI) of the head. Children are screened for ash-leaf macules using a Wood's light. The angiofibromas may be improved by hyfrecation or laser, but tend to recur. Genetic counselling is given once the diagnosis is made. The support group is helpful.

Incontinentia pigmenti

Incontinentia pigmenti is a rare X-linked dominant condition that is usually lethal in utero in males. In females, it presents within a few days of birth as a widespread blistering eruption (p. 13). Warty papules follow, but are replaced by hyperpigmentation, which appears in a whorled pattern. Skeletal, ocular, neurological and dental abnormalities are associated.

Xeroderma pigmentosum

Xeroderma pigmentosum is a group of rare autosomal recessive conditions characterized by defective repair of ultraviolet (UV)-damaged DNA. Photosensitivity begins in infancy, and freckles and keratoses appear on exposed skin in childhood. Squamous cell and basal cell carcinomas, keratoacanthomas and malignant melanomas subsequently develop in the UV-damaged skin (Fig. 48.5). Strict sunlight avoidance is necessary but, in its severe form, the disease can be fatal in the first or second decade. The gene loci are known (p. 13). Prenatal diagnosis is possible (p. 95) and is used when parents have already had one affected child.

Ehlers–Danlos syndrome

Ehlers–Danlos syndrome is a group of multisystem disorders of defective collagen structure and biochemistry (gene loci: p. 12). The diseases may be dominant, recessive or X-linked. Manifestations range from mild to severe and life-threatening. The skin, joints, blood vessels and internal organs are variably affected. The features include:

- elasticity of the skin
- joint hyperextensibility
- skin fragility with bruising and scarring (Fig. 48.6).

In the more severe types, aneurysms and rupture of large arteries may be found. The manifestations range from mild to severe and life-threatening.

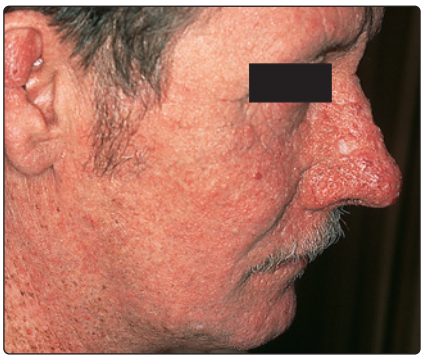


Fig. 48.5 Xeroderma pigmentosum. This patient shows severely sun-damaged skin with freckling, keratoses and scars from excision of tumours.

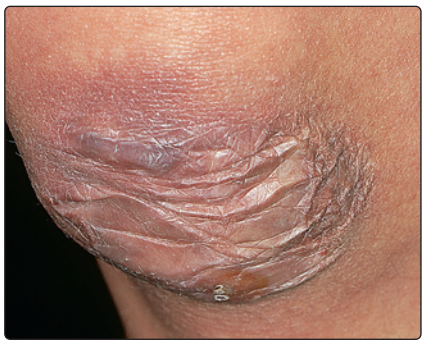


Fig. 48.6 Ehlers–Danlos syndrome. Ugly scarring has resulted from fragile skin and poor wound healing.

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum is a systemic disorder. The inheritance is autosomal recessive. The affected gene (chromosome 16) controls transmembrane peptide transport and results in calcified elastic fibres. The skin is loose, wrinkled and yellow and contains small papules (resembling xanthomas), giving a 'chicken skin' appearance. These changes are most obvious at the neck and flexures. Angioid streaks in the retina are seen in more than 50% of cases. Arterial involvement may result in gastrointestinal or cerebral haemorrhage.

The premature ageing syndromes

The features of ageing include an increased susceptibility to neoplasia, dementia, diabetes, autoimmune disease, cataracts, premature alopecia and hair greying, osteoporosis and degenerative vascular disease. *Down syndrome* shows several of these stigmata and is the most common condition in which premature ageing occurs. Many of the other disorders of premature ageing, such as *Werner syndrome* or *progeria*, are very rare and often show autosomal recessive inheritance.

Aged skin is dry, wrinkled, atrophic, shows loss of elasticity and uneven pigmentation and is susceptible to the development of benign and malignant tumours. Photoageing from chronic sun exposure (p. 113.e1) can produce similar changes, although certain of the features are more prominent. Some conditions, such as pseudoxanthoma elasticum or xeroderma pigmentosum, have the signs of aged skin without necessarily showing the more generalized features of ageing.

Neurocutaneous disorders and other syndromes

- **NF1 neurofibromatosis** is a relatively common autosomal dominant condition characterized by café-au-lait spots, dermal neurofibromas and often skeletal or neurological anomalies. The abnormal gene is on chromosome 17.
- **Tuberous sclerosis complex** is a not infrequent autosomal dominant disorder with prominent skin signs (e.g. facial angiofibromas and periungual fibromas), neurological problems (mental retardation and epilepsy) and ocular, cardiac and renal tumours.
- **Incontinentia pigmenti** is a rare X-linked dominant disease, present at birth, which evolves through vesicular and warty stages to leave whorled patterns of pigmentation. Skeletal, ocular and neurological defects are associated.
- **Xeroderma pigmentosum** represents a group of rare recessive conditions showing defects of DNA repair, characterized by skin tumours and premature death.
- **Ehlers–Danlos syndrome** is a group of inherited connective tissue disorders in which skin elasticity, scarring and joint hypermobility are found. Some types are life-threatening.
- **Pseudoxanthoma elasticum** is an inherited disease that results in calcification of elastin. The skin is wrinkled with yellowish papules and can sag in the flexures. Retinal angioid streaks are seen. Vascular signs and symptoms can occur.

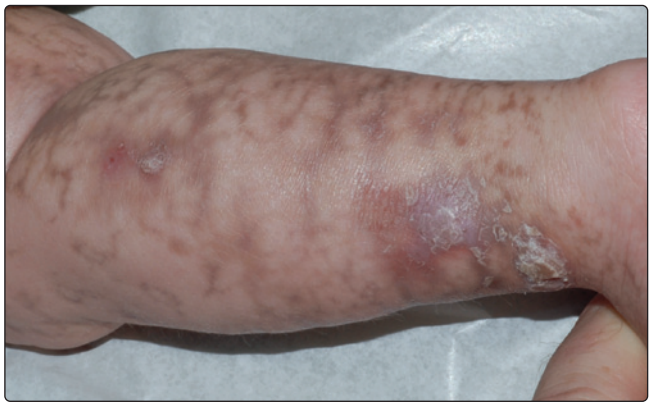


Fig. e48.1 Incontinentia pigmenti. Verrucous and hyperpigmented lesions in a streaky distribution on the leg of an infant with incontinentia pigmenti. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

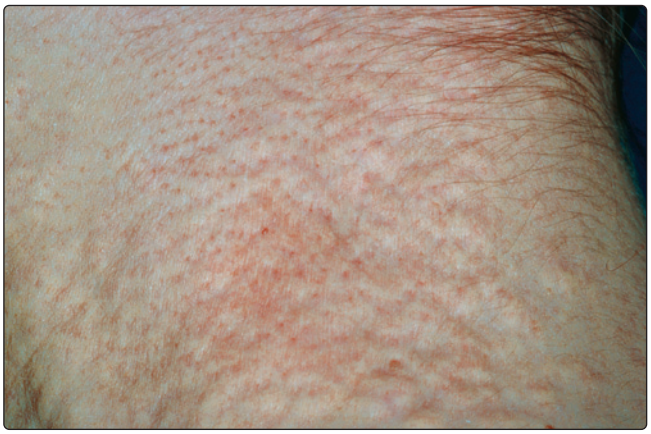


Fig. e48.2 Pseudoxanthoma elasticum. The sheets of small yellow-to-cream papules (here with some erythema) giving the plucked-chicken skin appearance are typical for pseudoxanthoma elasticum. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

The tuberous sclerosis gene shows wide variation of expression even in one family. The prognosis for a severely affected infant is poor and that for an older child or a young adult is unpredictable.

Incontinentia pigmenti is a rare X-linked dominant condition that is usually lethal in utero in males. In females, it presents within a few days of birth as a widespread blistering eruption (p. 13). Warty papules follow, but are replaced by hyperpigmentation, which appears in a whorled pattern (Fig. e48.1). Skeletal, ocular, neurological and dental abnormalities are associated.

Ehlers–Danlos syndrome is a group of multisystem disorders of defective collagen structure and biochemistry (gene loci: p. 12). These are separate and specific conditions that are distinct in features and, where it is known, genetic basis. The diseases may be dominant, recessive or X-linked. Manifestations range from mild to severe and life-threatening. The skin, joints, blood vessels and internal organs are variably affected. The features include:

Correct diagnosis allows targeted management, family screening and prenatal diagnosis.

Pseudoxanthoma elasticum is a systemic disorder. The inheritance is autosomal recessive. The affected gene (chromosome 16) controls transmembrane peptide transport and results in calcified elastic fibres. The skin is loose, wrinkled and yellow and contains small papules (resembling xanthomas), giving a 'chicken skin' appearance (Fig. e48.2). These changes are most obvious at the neck and flexures. Angioid streaks in the retina are seen in more than 50% of cases. Arterial involvement may result in gastrointestinal or cerebral haemorrhage.

Patient self-help organizations

Patients with neurofibromatosis can be assisted by the patient help groups, for example, The Neuro Foundation (access via http://www.nfauk.org/). The Tuberous Sclerosis Association can be very helpful to patients (access via http://www.tuberous-sclerosis.org).

Further reading – online sources

More information on neurocutaneous syndromes is available at the website of the National Centre for Biotechnology Information (access via http://www.ncbi.nlm.nih.gov/). More information on neurofibromatosis is available at the website the National Institute for Neurological Disorders and Stroke (http://www.ninds.nih.gov/disorders/).

Further reading – textbooks

Spritz, J.L., 2005. Genodermatoses, second ed. Lippincott Williams & Wilkins, Philadelphia, PA.
Tadini, G., Brena, M., Gelmetti, C., Pezzani, L., 2015. Atlas of Genodermatoses, second ed. CRC Press, Boca Raton, FL.

49 Benign tumours

Skin tumours are common, and their incidence is rising in Western countries (p. 25). The treatment of skin tumours makes up a large part of current dermatological practice (p. 24). Many skin tumours are benign, and these are described in this section. Viral warts, actinic keratoses and naevi are mentioned elsewhere.

Benign epidermal tumours

Seborrhoeic wart (basal cell papilloma)

A seborrhoeic wart (seborrhoeic keratosis) is a common, usually pigmented, benign tumour consisting of a proliferation of basal keratinocytes (Fig. 49.1). The cause is unknown, although they may be 'naevoid'. Seborrhoea is not a feature.

Clinical presentation

Seborrhoeic warts have the following features:

- often multiple (Fig. 49.2), sometimes solitary
- affect the elderly or middle-aged
- mostly found on the trunk and face
- generally round or oval in shape
- start as small papules, often lightly pigmented or yellow
- become darkly pigmented, warty nodules, 1–6 cm in diameter
- have a 'stuck-on' appearance, with keratin plugs and well-defined edges.

Differential diagnosis

The diagnosis is usually obvious from the physical findings and multiplicity of the lesions. Occasionally, a seborrhoeic wart can resemble an actinic keratosis, melanocytic naevus, pigmented basal cell carcinoma or malignant melanoma.

Management

Multiple lesions can be adequately dealt with using liquid nitrogen cryotherapy. Thicker seborrhoeic warts are best treated by curettage or shave biopsy, with cautery or hyfrecation. If there is diagnostic doubt, they can be excised. Histological examination is advised in all cases.

Skin tags

Skin tags are pedunculated, benign fibroepithelial polyps, a few millimetres in length. They are common, mainly seen in the elderly or middle-aged, and show a predilection for the neck, axillae, groin and eyelids (Fig. 49.3). The cause is unknown, but they are often found in obese individuals. Occasionally, skin tags are confused with small melanocytic naevi or seborrhoeic warts. The treatment, usually for cosmetic reasons, is by snipping the stalk with scissors or cutting through it with a hyfrecator (under local anaesthetic if necessary) or using cryotherapy.

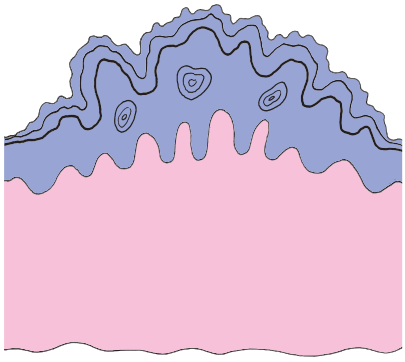


Fig. 49.1 Histopathology of seborrhoeic wart. This figure shows a hyperkeratotic epidermis, thickened by basal cell proliferation, with keratin cysts.

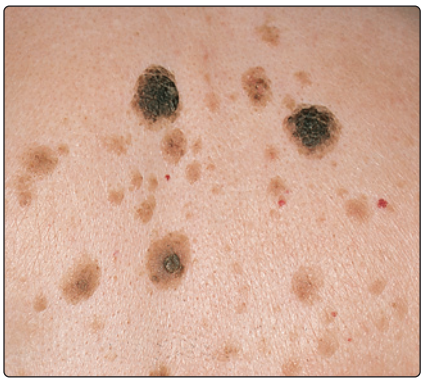


Fig. 49.2 Seborrhoeic warts on the trunk, with a few small Campbell-de-Morgan spots.

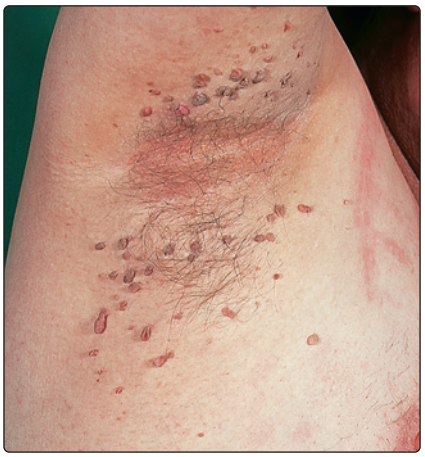


Fig. 49.3 Skin tags in the axilla.

Epidermal (epidermoid) cyst

Epidermal cysts, usually seen on the scalp, face or trunk, are sometimes incorrectly called sebaceous cysts. They are keratin-filled and derived from the epidermis or, in the case of the related pilar cyst, the outer root sheath of the hair follicle. The cysts are firm, skin coloured, mobile and normally 1–3 cm in diameter. Bacterial infection is a complication. Excision is curative.

Milium

Milia are mostly seen on the face, where they typically appear as small white keratin cysts (1–2 mm in size) around the eyelids and on the upper cheeks. They are often seen in children, but may appear at any age. Occasionally, milia may develop as part of healing after a subepidermal blister, e.g. with porphyria cutanea tarda. Milial cysts can normally be extracted using a sterile needle.

Benign dermal tumours

Dermatofibroma (fibrous histiocytoma)

Dermatofibromas are common dermal nodules, and are usually asymptomatic. Histologically, they show a proliferation of histiocytes and fibroblasts, with dermal fibrosis and sometimes epidermal hyperplasia. They possibly represent a reaction pattern to an insect bite or other trauma, although often no such history is obtained.

Clinical presentation

Dermatofibromas are usually seen in young adults, most commonly women, and mainly occur on the lower legs. They are firm, dermal nodules 5–10 mm in diameter and may be pigmented (Fig. 49.4). They enlarge slowly, if at all.

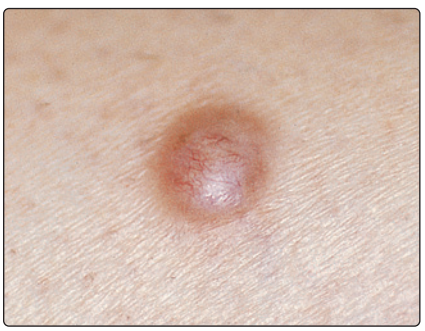


Fig. 49.4 Dermatofibroma on the lower leg.

Inflamed seborrhoeic warts can cause particular concern with regard to the possibility of malignant change (Fig. e49.1).

Milia are mostly seen on the face, where they typically appear as small white keratin cysts (1–2 mm in size) around the eyelids and on the upper cheeks (Fig. e49.2). They are often seen in children, but may appear at any age. Occasionally, milia may develop as part of healing after a subepidermal blister, e.g. with porphyria cutanea tarda. Milial cysts can normally be extracted using a sterile needle.

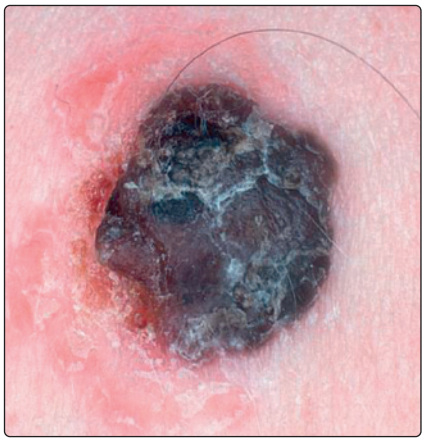


Fig. e49.1 An inflamed seborrhoeic wart, as shown here, may give rise to concern about the presence of malignant change. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

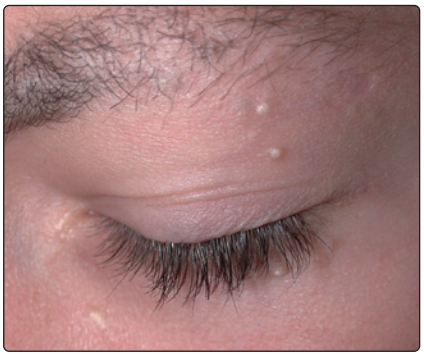


Fig. e49.2 Milia on the eyelid. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

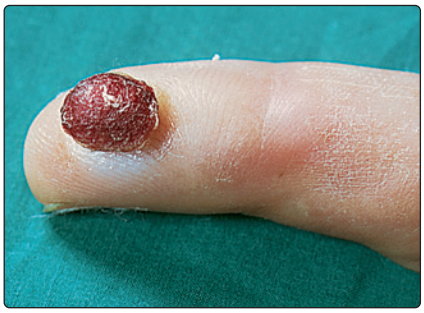


Fig. 49.5 Pyogenic granuloma on the finger.

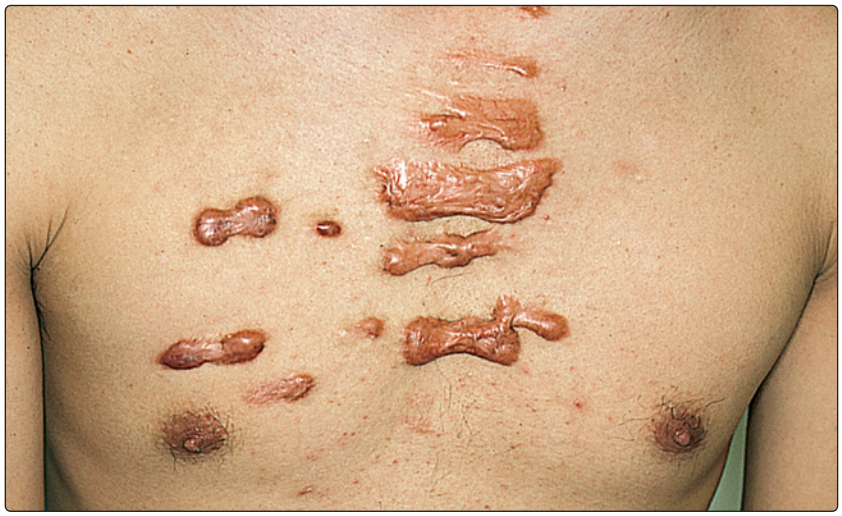


Fig. 49.6 Keloids. The nodules are seen on the chest of a patient with a history of acne.

Management

A pigmented dermatofibroma may be confused with a melanocytic naevus or a malignant melanoma. Excision of symptomatic or diagnostically doubtful lesions is recommended.

Pyogenic granuloma

A pyogenic granuloma is a rapidly developing bright red or blood-crusted nodule that may be confused with a malignant melanoma. It is neither pyogenic nor granulomatous, but is an acquired haemangioma.

Clinical presentation

A pyogenic granuloma typically:

- develops at a site of trauma, e.g. a prick from a thorn
- presents as a bright red, sometimes pedunculated, nodule 5–10 mm in diameter that bleeds easily (Fig. 49.5)
- enlarges rapidly over 2–3 weeks
- is seen on a finger (also on lip, face and foot)
- occurs in young adults and children.

Management

Curettage and cautery, or excision, is needed. The specimen is sent for histological examination to exclude a malignant melanoma. Not infrequently, a pyogenic granuloma may recur after curettage.

Keloid

A keloid is an excessive proliferation of connective tissue in response to skin trauma and differs from a hypertrophic scar because it extends beyond the limit of the original injury. Keloids show the following characteristics:

- present as protuberant and firm smooth nodules or plaques (Fig. 49.6).
- occur mainly over the upper back, neck, chest and ear lobes.
- develop more commonly in black Africans.
- have their highest incidence in the second to fourth decades.

Treatment is with a topical silicone sheet or gel, or steroid injection (p. 21).

Campbell-de-Morgan spot (cherry angioma)

Campbell-de-Morgan spots are benign capillary proliferations, commonly seen as small bright-red papules on the trunk in elderly or middle-aged patients (see Fig. 49.2). If necessary, they can be removed by hyfrecation or cautery.

Tumours of the skin appendages

Tumours of the skin appendages, i.e. of the eccrine and apocrine sweat ducts, hair follicles and sebaceous glands, are relatively rare. Clinically, they often present as rather nonspecific cutaneous nodules, and they are difficult to diagnose without histology following excision. Occasionally, these tumours are malignant.

Lipoma

Lipomas are benign tumours of fat, and present as soft masses in the subcutaneous tissue. They are often multiple and are mostly found on the trunk, neck and upper extremities. Sometimes they are painful. Removal is rarely needed.

Chondrodermatitis nodularis

Chondrodermatitis nodularis is not a neoplasm, but presents as a painful small nodule on the upper rim of the helix of the pinna, usually in elderly men (p. 123). It is due to inflammation in the cartilage that may be a response to degenerate dermal collagen induced by pressure or chronic sun exposure. They are often confused with basal cell carcinomas. Excision is curative.

Benign tumours

Lesion	Age at onset	Main features
Epidermal		
Viral wart	Childhood mainly	Usually on hands or feet (p. 54)
Actinic keratosis	Old age	Sun-exposed areas (p. 123)
Seborrhoeic wart	Old/middle age	Keratosis, often on trunk or face
Milia	Childhood	White cysts, often on face
Epidermal cyst	After childhood	Mostly on face or scalp
Skin tags	Middle/old age	Seen on neck, axillae and groin
Dermal		
Dermatofibroma	Young adult	Nodule, often on leg, F > M
Melanocytic naevus	Teens/young adult	Brown macule or papule (p. 100)
Cherry angioma	Old/middle age	Small red papule on trunk
Pyogenic granuloma	Child/young adult	Red nodule, often on finger
Keloid	Second–fourth decades	Chest/neck, affects black Africans
Lipoma	Any age	Soft tumour on trunk or limbs
Chondrodermatitis nodularis	Old/middle age	Nodule on upper pinna, M > F

Campbell-de-Morgan spots are benign capillary proliferations, commonly seen as small bright-red papules on the trunk in elderly or middle-aged patients (see Fig. 49.2 and Fig. e49.3). If necessary, they can be removed by hyfrecation or cautery.

Sebaceous hyperplasia

In sebaceous gland hyperplasia, small yellow dome-shaped papules, often with a small central umbilication, are seen on the mid-forehead, cheeks or nose (Fig. e49.4). They usually occur in the middle aged or elderly. Sometimes larger papules of sebaceous hyperplasia are confused with basal cell carcinomas. Histology shows hyperplastic lobules of mature sebaceous glands. There is no particular significance to sebaceous hyperplasia. Treatment may be requested for cosmetic reasons. Hyfrecation, laser treatment or cryotherapy may be tried. If lesions are extensive, some dermatologists have used oral isotretinoin.

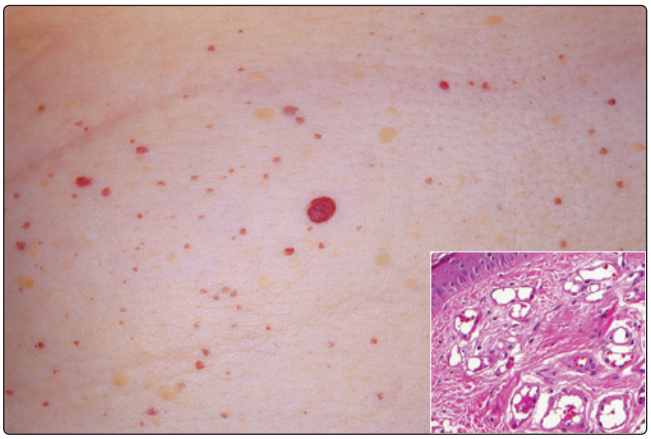


Fig. e49.3 Campbell-de-Morgan spots (cherry angiomas). Multiple small red papules of various diameters, representing Campbell-de-Morgan spots (cherry angiomas) are seen. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Benign tumours of the skin appendages

Besides those growths already mentioned, there are many types of benign tumour of the hair follicle, external root sheath, hair matrix, sebaceous gland, apocrine gland and eccrine sweat gland. Most are fairly uncommon and many are difficult to diagnose clinically, as they often present as relatively unspecified soft or firm red papules or nodules. Readers are referred to specialist texts for more information, but two of the more frequent benign skin appendage tumours are mentioned here: pilomatrixoma and syringoma.

Pilomatrixoma

Pilomatrixoma is a benign hamartomatous tumour of the hair matrix. It presents at any age, though often before the age of 20 years, as a solitary deep dermal or subcutaneous nodule on the head, neck or arms (Fig. e49.5). The tumour is often firm and of short duration. Excision with histological confirmation is curative.

Syringoma

Syringomas are usually multiple and most likely to have their first onset during adolescence (they can be recurrent). Syringomas are benign tumours of the eccrine ducts. They present as small skin-coloured or yellowish dermal papules (<3 mm in diameter) and tend to develop around the eyelids, cheeks, face or neck (Fig. e49.6). Treatment may be needed for cosmetic reasons. It is usual to take a biopsy for histological confirmation. Lesions may respond to hyfrecation or laser therapy.

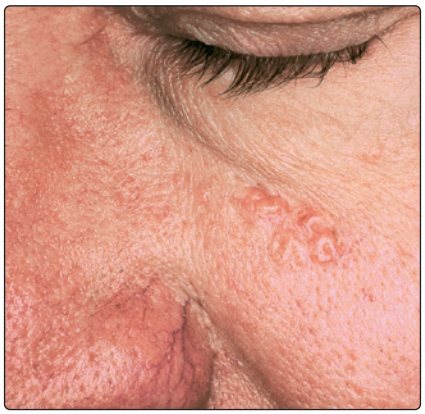


Fig. e49.4 Sebaceous hyperplasia. Small umbilicated papules of sebaceous hyperplasia are located on the cheek. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

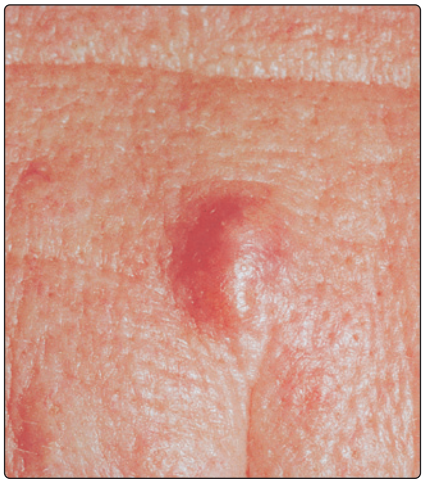


Fig. e49.5 A pilomatrixoma on the forehead, showing the typical rather non-specific appearance of an erythematous nodule. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

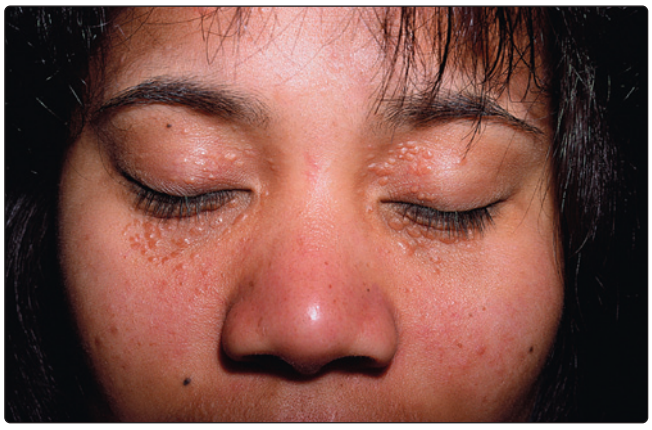


Fig. e49.6 Syringoma. A typical presentation of syringomas as small flesh-coloured papules a few millimetres in diameter, located around the upper and lower inner eyelids. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Further reading – online sources

The website of the American Association of Family Physicians has an excellent article on benign growths in the skin (access via http://s.aafp.org/).

Further reading – textbooks

For further information, readers are referred to a large diagnostic tome:

Habif, T.P., 2015. Clinical Dermatology: A Color Guide to Diagnosis and Therapy. Elsevier, Atlanta, GA.

50 Naevi

A naevus is a benign proliferation of one or more of the normal constituent cells of the skin. Naevi may be present at birth or may develop later. The commonest naevi are those containing benign collections of melanocytic naevus cells, but other types of naevus are found (Table 50.1). Vascular naevi are dealt with on page 121.

Table 50.1 **A classification of naevi**

Group	Example
Melanocytic	Congenital (p. 109) Junctional Intradermal Compound Spitz Blue Halo Becker's naevus Dysplastic (p. 109)
Vascular	Salmon patch (p. 121) Port-wine stain (p. 121) Strawberry (p. 121) Cavernous haemangioma
Epidermal	Warty naevus
Connective tissue	Tuberous sclerosis (p. 96)

Melanocytic naevi

Melanocytic naevi ('moles') are common. They are present in most Caucasoids but are less prevalent in Mongoloids and black Africans.

Aetiopathogenesis and pathology

The naevus cells in melanocytic naevi are thought to be derived from melanocytes that migrate to the epidermis from the neural crest during embryonic development (p. 3). The reason for the development of naevi is unknown, but they seem to be an inherited trait in many families.

The position of the naevus cells within the dermis determines the type of naevus (Fig. 50.1). The junctional type has clusters of naevus cells at the dermoepidermal junction, the intradermal type has nests of naevus cells in the dermis and the compound naevus shows both components.

Naevus cells produce melanin and, if the pigment is deep in the dermis, an optical effect can give the lesion a blue colour, as in a blue naevus.

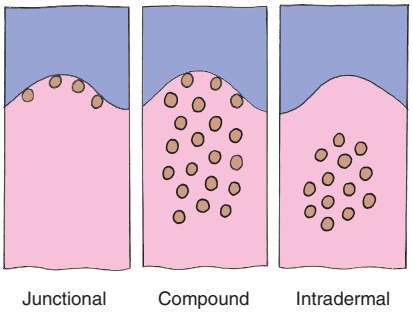


Fig. 50.1 Types of melanocytic naevus. The site of the naevus cells, either at the dermoepidermal junction or in the dermis, or at both places, determines the type of melanocytic naevus.

Clinical presentation

A congenital naevus, that is one present at or soon after birth, is seen in about 1–3% of infants, but most naevi develop during childhood or adolescence. Their number reaches a peak in the third decade, and they tend to become less numerous thereafter. However, it is not unusual to see a few new naevi appear after the third decade, especially if provoked by excessive sun exposure or pregnancy. The average young white adult has between 20 and 50 melanocytic naevi. Dermoscopy is helpful in assessment (p. 20). The clinical features of different types of naevus are as follows:

- *Congenital naevi*. Present at or shortly after birth, they are usually more than 1 cm in size, vary in colour from light brown to black and often become protuberant and hairy. They can be disfiguring, as in the rare bathing trunk naevus, and carry a lifetime risk of up to 5% for the development of malignant melanoma (p. 109).
- *Junctional naevi*. These are flat macules, varying in size from 2 to 10 mm and in colour from light to dark brown (Fig. 50.2). They are usually round or oval in shape and have a predilection for the palms, soles and genitalia.
- *Intradermal naevi*. The intradermal naevus is a dome-shaped papule or nodule that may be skin coloured or pigmented, and is most often seen on the face or neck.
- *Compound naevi*. Compound naevi are usually <10 mm in diameter, have a smooth surface and vary in their degree of pigmentation (Fig. 50.3). Larger lesions may develop a warty or cerebriform appearance. They may occur anywhere on the skin surface.
- *Spitz naevi*. A Spitz naevus is a firm, reddish–brown, rounded nodule seen typically on the face or leg of a child. The initial growth may be rapid. Histologically, the naevus cells are proliferative, and the dermal blood vessels are dilated. Differentiation from malignant melanoma is important.
- *Blue naevi*. This variant, so-called because of its steely-blue colour, is usually solitary and is most common on the extremities, particularly the hands and feet.
- *Halo naevi*. Halo (or Sutton's) naevi are mainly seen on the trunk in children or adolescents and represent the destruction, by the body's immune system, of naevus cells in a naevus. A white halo of depigmentation surrounds the pre-existing naevus that subsequently involutes (Fig. 50.4). This may be due to anti-melanocyte autoimmune attack. There is an association with vitiligo. Multiple halo naevi often appear simultaneously.
- *Becker's naevi*. This rare variant usually develops in adolescent males as a unilateral lesion on the upper back or chest (Fig. 50.5). Hyperpigmented at first, it later becomes hairy and is prone to acne. It may represent mosaicism.
- *Dysplastic naevi*. Dysplastic (atypical) naevi show some irregularity in outline and in pigmentation (p. 103).

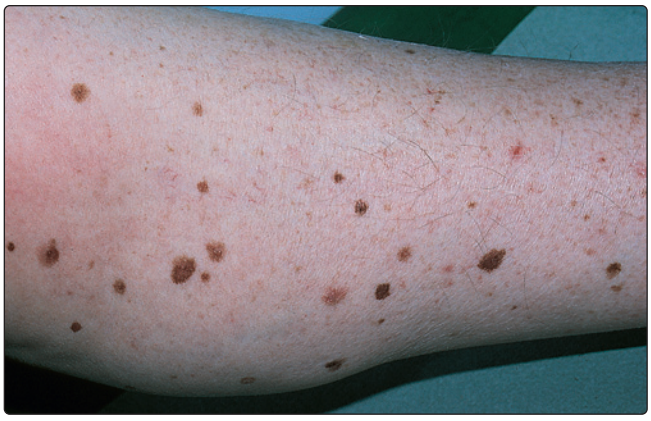


Fig. 50.2 Multiple junctional (and compound) naevi on the lower leg.

- *Intradermal naevi*. The intradermal naevus is a dome-shaped papule or nodule that may be skin coloured or pigmented, and is most often seen on the face or neck (Fig. e50.1).
- *Compound naevi*. Compound naevi are usually <10 mm in diameter, have a smooth surface and vary in their degree of pigmentation (Fig. 50.3 and Fig. e50.2). Larger lesions may develop a warty or cerebriform appearance. They may occur anywhere on the skin surface.
- *Spitz naevi*. A Spitz naevus is a firm, reddish–brown, rounded nodule seen typically on the face or leg of a child (Fig. e50.3). The initial growth may be rapid. Histologically, the naevus cells are proliferative, and the dermal blood vessels are dilated. Differentiation from malignant melanoma is important.
- *Blue naevi*. This variant, so-called because of its steely-blue colour, is usually solitary and is most common on the extremities, particularly the hands and feet (Fig. e50.4).

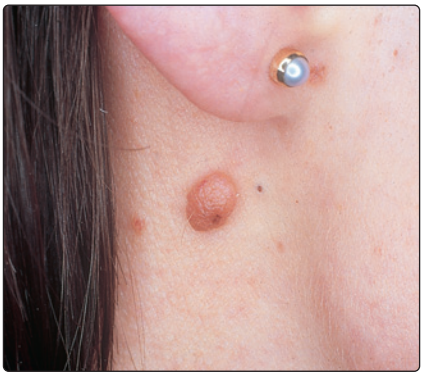


Fig. e50.1 A predominantly intradermal melanocytic naevus on the neck showing a smooth dome-shaped surface and light pigmentation. The fleck of darker pigmentation warrants closer examination using a dermoscope. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

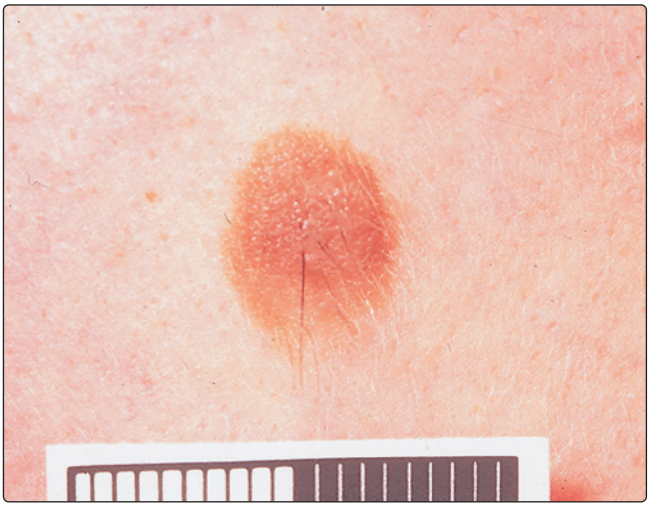


Fig. e50.2 A lightly pigmented compound melanocytic naevus. The border is rather indistinct. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

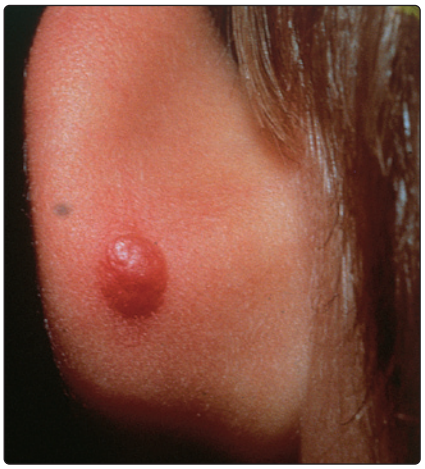


Fig. e50.3 A Spitz naevus showing the typical appearance of a reddish-brown, rounded, smooth-surfaced nodule. The histology shows proliferating naevus cells. Differentiation from malignant melanoma may be problematic. Some pathologists regard certain Spitz naevi as malignant. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

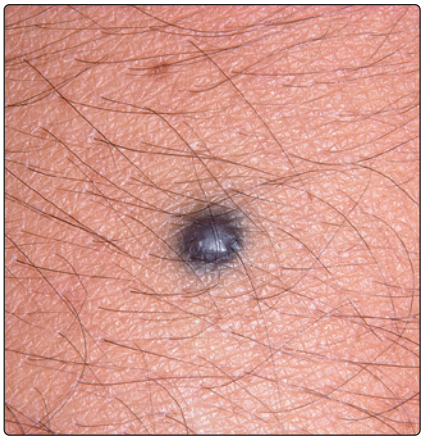


Fig. e50.4 A cellular blue naevus. In this instance, a blue-black papule is evident. The histological features are of aggregates of dendritic heavily pigmented melanocytes in the lower dermis. The onset is often in childhood or adolescence. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

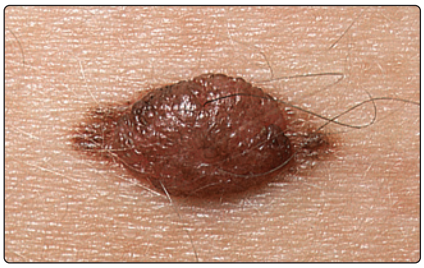


Fig. 50.3 A compound melanocytic naevus.

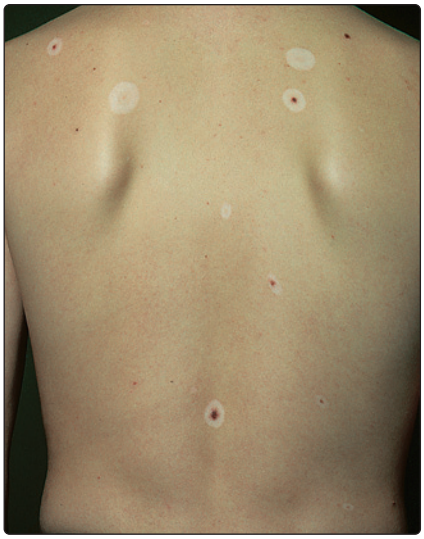


Fig. 50.4 Multiple halo naevi on the back of an adolescent.

Management

Over recent years, publicity in the media and in public health campaigns has promoted the early diagnosis of malignant melanoma. This has led to a greater public awareness about the significance of change in pigmented lesions, and many patients are now referred because of concern about their 'moles'. Any change merits serious attention (p. 108). The differential diagnosis of melanocytic naevi is shown in Table 50.2. Naevi are excised because of:

- *concern about malignancy*, e.g. recent increase in size or itching
- *an increased risk of malignant change*, e.g. in a large congenital naevus
- *cosmetic reasons*, e.g. ugly naevi, usually on the face or neck
- *repeated inflammation*, e.g. bacterial folliculitis, often in hairy facial naevi
- *recurrent trauma*, e.g. naevi on the back that catch on bra straps.

All excised naevi should be sent for histology. Some clearly benign protuberant naevi that require removal for cosmetic reasons can be dealt with by shave biopsy (p. 115).

Epidermal naevi

Epidermal naevi are usually present at birth or develop in early childhood. They are warty, often pigmented and frequently linear (Fig. 50.6). Most are a few centimetres long, but they can be much larger and involve the length of a limb or the side of the trunk. They can be excised, but recurrence is common. A variant on the scalp, *naevus sebaceus*, carries a risk of malignant transformation and should be excised.

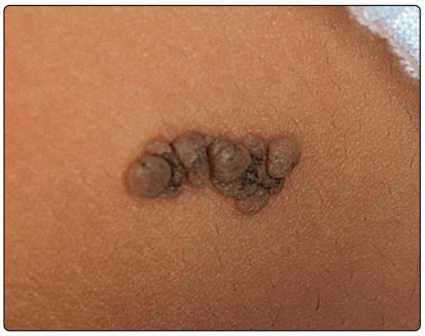


Fig. 50.6 An epidermal naevus on the thigh.

Connective tissue naevi

Connective tissue naevi are rare. They appear as smooth, skin-coloured papules or plaques and may be multiple. Coarse collagen bundles are seen in the dermis on histology. An example is the collagen-containing cobblestone naevus (shagreen patch) seen in tuberous sclerosis (p. 97).

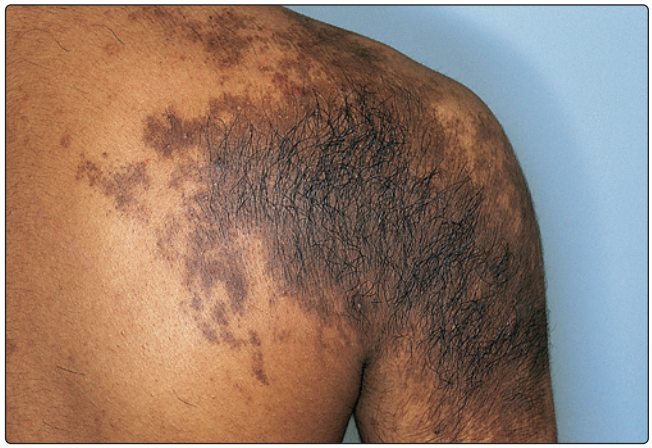


Fig. 50.5 A Becker's naevus on the shoulder of a young man.

Table 50.2 **Differential diagnosis of melanocytic naevi**

Lesion	Distinguishing features
Freckle	Tan-coloured macules on sun-exposed sites (p. 79)
Lentigine	Usually multiple, onset in later life (p. 79)
Seborrhoeic wart	Stuck-on appearance, warty lesions, may show keratin plugs, but easily confused (p. 98)
Haemangioma	Vascular but may show pigmentation
Dermatofibroma	On legs, elevated nodule, firm and pigmented (p. 99)
Pigmented basal cell carcinoma	Often on face, pearly edge, increase in size, can ulcerate, other photodamage may coexist
Malignant melanoma	Variable colour and outline, may have increased in size, be inflamed, bleed or be itchy (p. 108)

Naevi

- **Melanocytic naevi** are very common, usually multiple, pigmented and benign. They appear during childhood or adolescence. Young white adults have 20–50. Variants include:
  - *congenital naevi*: present at birth, may be protuberant or hairy and have a small risk of malignant change
  - *junctional naevi*: flat macules, often round or oval. Typically found on soles, palms or genitalia
  - *intradermal naevi*: dome-shaped, usually skin-coloured papules. Typically seen on the face
  - *compound naevi*: pigmented nodules or papules, sometimes warty or hairy. Histology shows junctional and dermal components
  - *Spitz naevi*: firm reddish–brown nodules typically seen on the face or legs in children
  - *blue naevi*: steely-blue in colour due to melanin in the deep dermis. They are mainly solitary and found on the extremities
  - *halo naevi*: show depigmentation where a naevus has involuted due to autoimmune attack. Mostly seen on the trunk
  - *Becker's naevi*: pigmented hairy lesions on the upper back or chest, usually in males and appearing in adolescence.
- **Epidermal naevi** are warty, pigmented and often linear. Usually small, they are sometimes extensive. A scalp variant, *naevus sebaceus*, should be excised as it has malignant potential.
- **Connective tissue naevi** are skin-coloured papules composed of coarse collagen in the dermis. They can occur as cobblestone naevi (shagreen patches) in tuberous sclerosis.

Epidermal naevi are usually present at birth or develop in early childhood. They are warty, often pigmented and frequently linear (Fig. 50.6). Most are a few centimetres long, but they can be much larger and involve the length of a limb or the side of the trunk. They can be excised, but recurrence is common. A variant on the scalp, *naevus sebaceus*, carries a risk of malignant transformation and should be excised (Fig. e50.5).

Connective tissue naevi are rare. They appear as smooth, skin-coloured papules or plaques and may be multiple (Fig. e50.6). Coarse collagen bundles are seen in the dermis on histology. An example is the collagen-containing cobblestone naevus (shagreen patch) seen in tuberous sclerosis (p. 97).

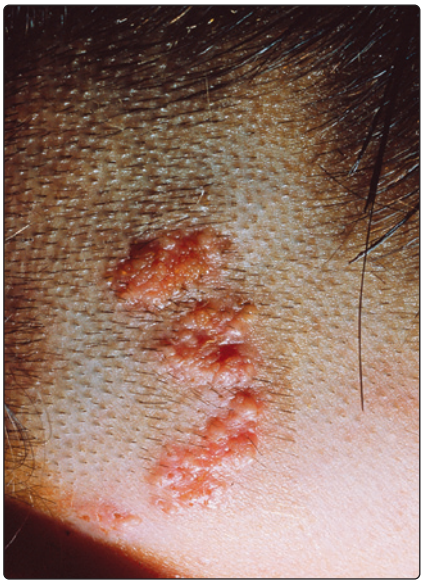


Fig. e50.5 *Naevus sebaceus* showing a characteristic appearance of confluent skin-coloured papules arranged in a semi-linear distribution on the scalp. Excision is required in view of the potential for the development of basal cell carcinoma or related tumours. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

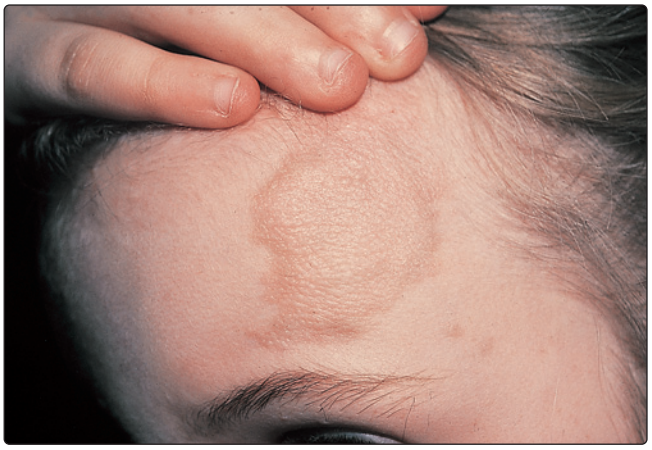


Fig. e50.6 A connective tissue naevus (shagreen patch) on the forehead showing the typical features of a raised yellowish-brown plaque with the suggestion of a cobblestone surface. These lesions are often located in the lumbosacral region. *(From Callen JP, Jorizzo JL, Bolognia JL, Piette WW, Zone JJ 2003 Dermatological Signs of Internal Disease, 4th edition. Saunders, with permission.)*

Further reading – online sources

Further details on melanocytic naevi can be found through the Medscape website (access via http://emedicine.medscape.com/). The website of the Primary Care Dermatology Society has a series of excellent photographs of different presentations of melanocytic naevi (access via http://www.pcds.org.uk/).

Further reading – textbooks

Further information on naevi is available in a specialist tome:

Crowson, A.N., Magro, C.M., Mihm, M.C., 2014. The Melanocytic Proliferations: A Comprehensive Textbook of Pigmented Lesions. Wiley, Hoboken, NJ.

51 Skin cancer – Premalignant disorders

Premalignant disorders in the skin are those which, if left untreated, may become skin cancers. The most important cancers with pre-cancerous states include squamous cell carcinoma (*actinic keratosis*; syn. solar keratosis) and melanoma (*dysplastic naevus*), although it is important to note that the risk of pre-cancerous lesions progressing to cancer is low.

Actinic keratoses

Aetiopathogenesis

Actinic keratoses are induced by chronic exposure to ultraviolet (UV) radiation. Histologically, they show hyperkeratosis, abnormal keratinocytes with loss of maturation and dermal elastosis. UVB causes direct DNA damage and this can suppress the function of tumour suppressor genes (especially p53), leading to increased cell proliferation. UV damaged keratinocytes become clonal and proliferate while failing to undergo typical maturation in the epidermis, which results in histological dysplasia. Thus, some experts recommend that this is best described as keratinocytic intraepidermal neoplasia (KIN), classified as mild, moderate or severe (grades 1–3), in line with other classifications such as cervical intraepidermal neoplasia. Complete replacement of the epidermis by atypical (dysplastic) keratinocytes without invasion through the basement membrane represents squamous cell carcinoma *in situ* (Bowen's disease; Ch. 53), while invasion through the basement membrane constitutes progression to squamous cell carcinoma (Ch. 53).

Actinic keratoses may regress spontaneously. Although the exact long-term risk of any individual actinic keratosis progressing to a squamous cell carcinoma has not been determined, it is estimated that this is low and may represent up to 0.53% per lesion per year. As it is not possible to identify which actinic keratosis is at risk of progression, the consensus is that treatment is necessary.

Risk factors for actinic keratosis include:

- old age
- male sex
- cumulative sun exposure
- fair skin
- immunosuppression, e.g. in renal transplant patients (p. 59)
- genetic factors (e.g. albinos, xeroderma pigmentosum, p. 78).

Clinical presentation

Actinic keratoses are scaly, roughened patches, usually <1 cm in diameter, found on sun-exposed skin and are often easier to palpate than to see (Fig. 51.1). They are almost only found on white-skinned individuals, and typically show a pinkish colour, but may be red or skin coloured. Typical sites include the forehead, nasal bridge, tops of the ears and dorsal hands. Severely affected individuals will often show 'field damage', which describes whole anatomical areas (e.g. forehead) affected by multiple extensive actinic keratoses (Fig. 51.2). Surrounding skin will usually show signs of chronic UV exposure such as telangiectasia, solar elastosis (wrinkles), solar lentigos and dyspigmentation. Clinical and histological subtypes have been described including pigmented, bowenoid, hyperkeratotic, atrophic and lichenoid actinic keratoses.

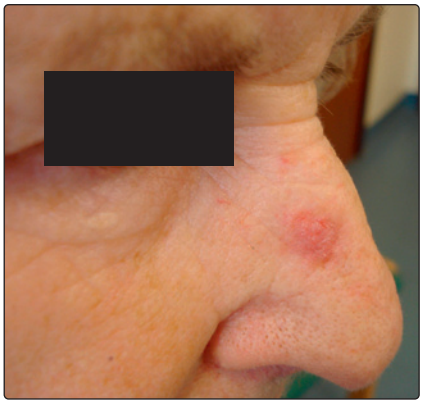


Fig. 51.1 An actinic keratosis.

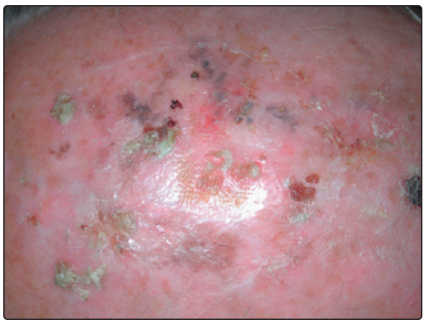


Fig. 51.2 Multiple actinic keratoses on the scalp.

Differential diagnosis

An actinic keratosis needs to be distinguished from in situ SCC (Bowen's disease), squamous cell carcinoma, keratoacanthoma, superficial BCC and seborrhoeic keratosis. Biopsy is rarely needed to confirm the diagnosis, and it is important to recognize that a biopsy from the margin of a squamous carcinoma may only show actinic keratosis histology. Similarly, shave biopsies capturing only epidermal histology, which show actinic keratosis change, may not easily exclude squamous cell carcinoma because of the lack of dermis in the specimen. Therefore, clinicopathological correlation is critical for biopsies showing actinic keratosis.

Management

It is important to advise about careful photoprotection for all cases with actinic keratoses. A variety of treatment options are available for the management of actinic keratoses.

Topical therapy

Diclofenac gel can be used for mild lesions, but requires twice daily treatment for 60–90 days. 5-fluorouracil cream, in various concentrations, applied daily for 1–4 weeks, or with salicylic acid (for more hyperkeratotic lesions) for 6–12 weeks, is an effective approach. Patients must be warned about the likely inflammatory reaction during therapy (Fig. 51.3). Imiquimod cream may also cause an inflammatory reaction and is available in various concentrations with

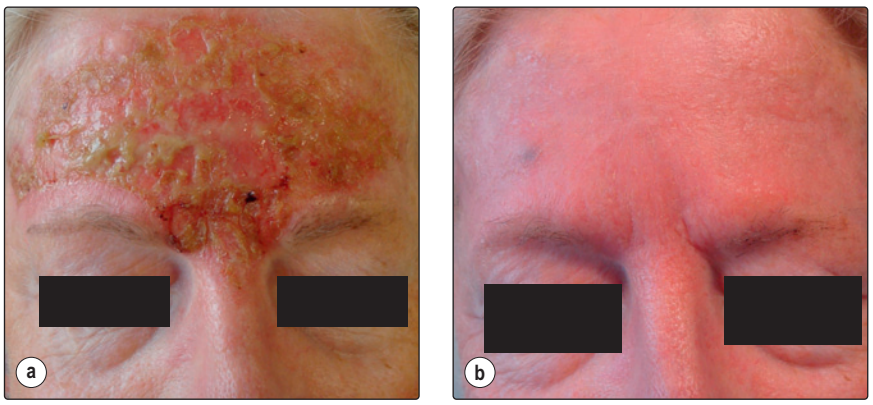


Fig. 51.3 (a) A severe inflammatory reaction following treatment of actinic keratoses with 5-fluorouracil cream and (b) recovery after 2 weeks.

slightly different frequencies of application. More recently, ingenol mebutate gel at different concentrations (depending on body site treated) has been shown to be effective in only two or three applications, without significant increase in inflammation.

Photodynamic therapy

This process requires application of a cream which overloads the keratinocyte haem biosynthetic pathway resulting in excess production of photosensitive porphyrins, thus on light exposure, release of intracellular oxygen free radicals causes cellular destruction. The process can be quite painful and requires curettage of thicker lesions to allow tissue penetration of the cream. Recent work has identified a variety of light sources that can be used, including natural daylight.

Cryotherapy

This treatment involves the application (usually by fine spray) of liquid nitrogen to the lesion. Care needs to be taken to ensure accurate treatment and minimal damage. Immediately following the procedure, the area will become inflamed and sore, but typically should settle over the course of a week with desquamation of the keratotic cells.

Surgical curettage/excision is only recommended for treatment resistant lesions, and in those where squamous cell carcinoma is suspected. Tender lesions or those displaying a keratin horn are best treated by surgical excision for this reason.

Dysplastic naevi

Diagnostic features

Dysplastic naevi show histological evidence of a proliferation of cytologically atypical melanocytes, in an atypical pattern, with an inflammatory host response. However, many of these features may be identified in clinically 'normal' melanocytic naevi. Previous studies have shown that in clinically atypical naevi >5 mm, approximately 70% will show histological atypia, whereas in clinically typical naevi >5 mm, approximately 50% will show histological atypia. Reliable clinical correlates with histological dysplasia are therefore lacking, but clinical and dermoscopic features of dysplasia include abnormalities in any of the ABCD criteria, e.g. asymmetry and irregularity of border and colour (Fig. 51.4). Typically dysplastic naevi, do not change (criterion E).

Aetiopathogenesis

Dysplastic naevi, by definition, are only confirmed by histological analysis and cannot be diagnosed by clinical appearance. Therefore, because all confirmed dysplastic naevi must have been excised, definitive assessment of the risk of progression from dysplastic naevus to melanoma is lacking. Although individuals with dysplastic naevi are clearly at increased risk of melanoma, the exact risk of progression within the same lesion from a dysplastic naevus to melanoma is a controversial area. Recent work shows that dysplastic naevi generally lack the genetic changes that associate with melanoma development, suggesting that they are a different entity.

Risk factors for dysplastic naevi include:

- Genetic factors (family history)
- Fair skin

Differential diagnosis

Dysplastic naevi are benign entities, but the clinical differential diagnosis for an atypical naevus is melanoma. Differentiation can be difficult, and in such cases, lesions are best excised. On some occasions, histological analysis may not clearly distinguish between dysplastic naevus and melanoma. In such cases, the recommended approach is to manage, as for melanoma, with re-excision of the scar (p. 109).

Management

Clinically, atypical naevi are a risk factor for melanoma, but as discussed earlier, the risk of an individual lesion progressing to melanoma is thought to be low. Therefore, the most important clinical decision is whether an individual lesion may represent melanoma (p. 108). After excision, dysplastic naevi diagnosed histologically do not require any further treatment but incompletely excised lesions are generally re-excised to gain complete removal. Patients with multiple atypical or dysplastic naevi need to be aware of their increased risk of melanoma and be advised appropriately.

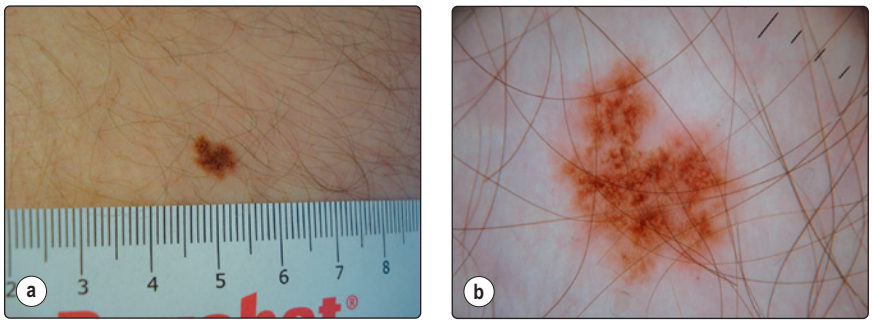


Fig. 51.4 Dysplastic naevus. (a) Clinical and (b) dermoscopic view.

Skin cancer – premalignant disorders

Actinic keratoses

- **Actinic keratosis** is a premalignant skin lesion induced by chronic ultraviolet exposure.
- **Actinic keratoses** are often multiple and may require treatment of large areas of sun-exposed skin.
- **Squamous cell carcinoma** can develop in sites of actinic keratoses, and must be considered in enlarging or tender lesions.
- **Actinic keratoses** can be treated by a variety of modalities including:
  - topical therapy
  - cryotherapy
  - photodynamic therapy
  - surgery

Dysplastic naevi

- '**Dysplastic naevus**' is a term used to describe histological atypia in a melanocytic proliferation. However, histological atypia features do not correlate well with clinical atypia. Therefore, clinically atypical naevi should not be referred to as dysplastic, unless confirmed by excision and histological analysis.
- The presence of **dysplastic naevi** is a risk factor for melanoma.
- **Dysplastic naevi** themselves have uncertain malignant potential and are probably, at worst, low risk for progression into melanoma.
- **Dysplastic naevi** need to be differentiated from melanoma, which may require surgical excision for confirmation.

Dysplastic naevi show histological evidence of a proliferation of cytologically atypical melanocytes, in an atypical pattern, with an inflammatory host response. However, many of these features may be identified in clinically 'normal' melanocytic naevi. Previous studies have shown that in clinically atypical naevi >5 mm, approximately 70% will show histological atypia, whereas in clinically typical naevi >5 mm, approximately 50% will show histological atypia. Reliable clinical correlates with histological dysplasia are therefore lacking, but clinical and dermoscopic features of dysplasia include abnormalities in any of the ABCD criteria, e.g. asymmetry and irregularity of border and colour (Fig. 51.4 and Fig. e51.1). Typically dysplastic naevi, do not change (criterion E).

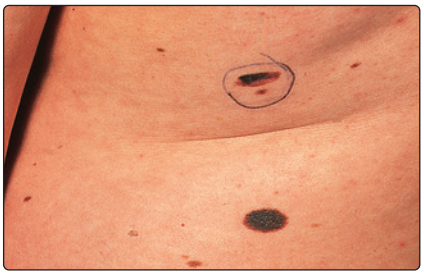


Fig. e51.1 Atypical naevus syndrome. This condition, which may be familial, is characterized by large numbers of atypical and 'dysplastic' naevi, many of which are often over 7 mm in diameter with an irregular edge and variable pigmentation. Affected individuals have an increased risk of developing malignant melanoma. They should avoid the sun and be closely observed. Changing or suspicious pigmented lesions should be excised for histological examination.

Further reading – online sources

More information on actinic keratoses and dysplastic naevi can be found at the Medscape website (access via http://emedicine.medscape.com).

Further reading – textbooks

There are many textbooks devoted to skin cancer management.

Bolognia, J.L., Jorizzo, J.L., Schaffer, J.V. (Eds.), 2012. Dermatology, third ed. Elsevier Saunders, Philadelphia.

Burns, T., Breathnach, S., Cox, N., Griffiths, C. (Eds.), 2010. Textbook of Dermatology, eighth ed. Blackwell, Oxford.

52 Skin cancer – Basal cell carcinoma

Malignant skin tumours are among the most common of all cancers. They are more frequent in light-skinned races, and ultraviolet (UV) radiation seems to be involved in their aetiology. The incidence of *non-melanoma skin cancer* in Caucasoids in the USA was recently estimated at 230/100 000 per year, compared with 3/100 000 for African Americans. The majority of malignant skin tumours (Table 52.1) are epidermal in origin and are either basal cell or squamous cell carcinomas (p. 104) or malignant melanomas (p. 106). Premalignant epidermal conditions are common (Ch. 51), but dermal malignancies are comparatively rare.

Table 52.1 **A classification of malignant skin tumours and premalignant conditions**

Cell origin	Premalignant condition (Ch. 51)	Malignant tumour
Keratinocyte	Actinic keratosis, in situ squamous cell carcinoma	Basal cell carcinoma, squamous cell carcinoma
Melanocyte	Dysplastic naevus	Malignant melanoma (p. 108)
Fibroblast		Dermatofibrosarcoma (p. 110.e2)
Lymphocyte		Lymphoma (p. 110)
Endothelium		Kaposi's sarcoma (p. 58)
Non-cutaneous		Secondary spread (metastasis)

Basal cell carcinomas

Basal cell carcinomas (BCC, rodent ulcers) are the commonest form of skin cancer and are typically seen on the face in elderly or middle-aged patients. Although there is strong epidemiological evidence for the role of UV radiation in the pathogenesis of BCCs, the tumours do not frequently occur on the most sun-damaged sites. They arise from the basal keratinocytes of the epidermis, are locally invasive, but very rarely metastasize.

Aetiopathogenesis

Malignant transformation of basal cells may be induced by:

- prolonged UV exposure (and acute sunburn)
- immunosuppression (e.g. renal transplant recipients)
- arsenic ingestion, e.g. in 'tonics' or drinking water
- X-rays and other ionizing radiation
- chronic scarring, e.g. burns or vaccination scars
- genetic predisposition, e.g. Gorlin syndrome (basal cell naevus syndrome).

Basal cell carcinomas are most common in those with fair 'Celtic' skin who live near the equator, and are seen more in males than in females. In the UK, they mainly occur in those over the age of 40 years, although, in Australia, they may be seen in the third decade.

Pathology

The tumour is classically composed of uniform basophilic cells, in well-defined islands, that invade the dermis from the epidermis as buds, lobules or strands (Fig. 52.1).

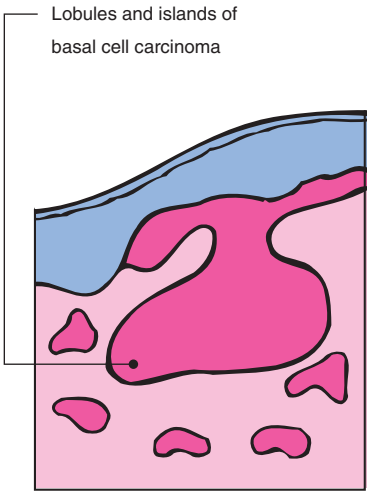


Fig. 52.1 The histological structure of a basal cell carcinoma.

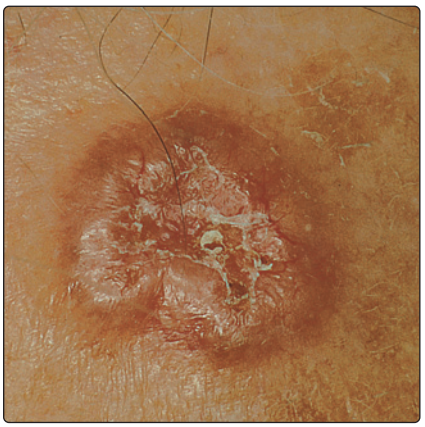


Fig. 52.2 Basal cell carcinoma. The lesion shows the typical pearly edge, telangiectasia and central crusting.

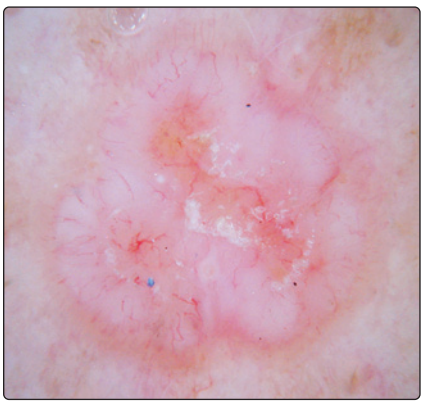


Fig. 52.3 Dermoscopic view of basal cell carcinoma. Note the arborizing telangiectasia.

Clinical presentation

Basal cell carcinomas occur mainly on light-exposed sites, commonly around the nose, the inner canthus of the eyelids and the temple. They grow slowly but relentlessly, are locally invasive and may destroy cartilage, bone and soft tissue structures. A lesion has often been present for 2 years or more before the patient seeks advice. Often, more than one tumour is evident. There are four main types of basal cell carcinoma, all of which may occasionally be pigmented:

1. *Nodular*. This is the commonest type of lesion and usually starts as a small, skin-coloured papule that shows fine telangiectasia and a glistening pearly edge (Fig. 52.2). Central necrosis often occurs and leaves a small ulcer with an adherent crust. The lesions are mostly <1 cm in diameter, but grow larger if present for several years. Clinically, they usually present as a thickened plaque rather than a tumour and, although firm to palpation, this may be difficult to establish in smaller lesions. Nodular BCCs often have slightly raised margins with a central depression. Superficial branching telangiectasia are characteristic and are seen on dermoscopy as 'arborizing' (Fig. 52.3). Stretching the skin between two fingers will often accentuate the margins giving them a pale white 'pearly' colour.

2. *Cystic*. These become tense and translucent and show cystic spaces on histology.
3. *Superficial*, often multiple, are multicentric and plaque-like. Lesions several centimetres in diameter are sometimes seen especially on the trunk (Fig. 52.4). They have a rim-like edge and are frequently lightly pigmented.
4. *Morphoeic*. This scar-like variant, most common on the face, often shows a white or yellow morphoea-like plaque that may be centrally depressed (Fig. 52.5).

Gorlin syndrome is a rare inherited predisposition for BCCs, where individuals suffer from multiple basal cell carcinomas from a young age (often early teens). Other clinical features such as mandibular bone cysts, palmar pits, rib anomolies, broad forehead and calcified falx cerebri may aid the diagnosis. Most individuals show mutations in *PTCH1*. Lesions may resemble small compound melanocytic naevi but are histologically typical basal cell carcinomas. Over time many lesions arise, predominantly on the head, neck and upper trunk. In severe cases, the extent and number of BCCs may make surgical approaches very challenging or impractical.

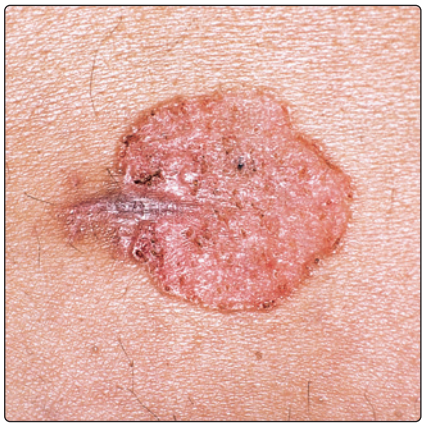


Fig. 52.4 Basal cell carcinoma of the superficial multifocal type. This was located on the trunk. A biopsy (scar visible) confirmed the diagnosis.

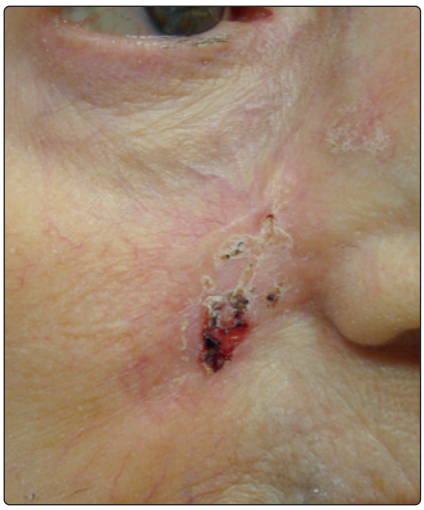


Fig. 52.5 Basal cell carcinoma of the right cheek in an immunosuppressed patient. This BCC has poorly defined clinical margins and is sited in a high-risk area. Discussion of planned management with a multidisciplinary team including a dermatological surgeon, plastic and maxillofacial surgeon and radiotherapist would be ideal.

Differential diagnosis

The differential diagnosis depends on the type, pigmentation and location of the basal cell carcinoma:

- *Nodular/cystic*: intradermal naevus (p. 100), molluscum contagiosum (p. 55), keratoacanthoma (p. 106), squamous cell carcinoma, sebaceous hyperplasia (a benign proliferation of sebaceous glands).
- *Superficial*: discoid eczema (p. 40), psoriatic plaque (p. 28), in situ squamous cell carcinoma (p. 106).
- *Morphoeic*: morphoea (p. 85), scar.
- *Pigmented*: malignant melanoma (p. 108), seborrhoeic wart (p. 98), compound naevus (p. 100).

Management

The most appropriate treatment for any one tumour depends on its size, site, type and the patient's age. If possible, complete *excision* is the best treatment, as this allows a histological check on the adequacy of removal. If excision is difficult, *radiotherapy* is suitable for those aged ≥60 years. Large tumours around the eye (Fig. 52.6) and the nasolabial fold, especially if of the morphoeic type, are best managed by surgical excision. *Mohs micrographic surgery* (p. 117) may be employed, as the margins of these tumours are often difficult to determine and may be extensive. *Curettage and cautery* is sometimes used for lesions on the trunk or upper extremities. Topical *imiquimod* (also unlicensed 5-fluoruracil) and photodynamic therapy are good treatments for superficial BCCs, but patients need to be pre-warned about the inflammatory reaction and discomfort of the treatment. Cryosurgery is now less widely used but may be useful if repeated topical applications are difficult e.g. on the back.

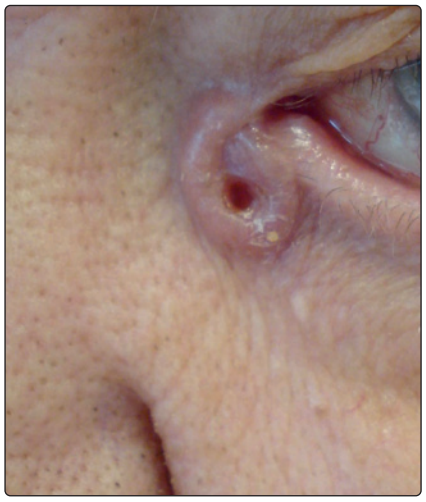


Fig. 52.6 Basal cell carcinoma of the lower lid. These lesions require careful surgical management to protect the lacrimal anatomy and prevent scar-induced retraction of the eyelid margin.

The recurrence rate is about 5% at 5 years for most methods of treatment. Follow-up is particularly important if there is concern about the adequacy of treatment. *Vismodegib*, a smoothened inhibitor, is useful for severe Gorlin's syndrome, inoperable, or metastatic BCCs.

Basal cell carcinoma

- **Basal cell carcinoma** (rodent ulcer) is a common tumour often seen on the face of elderly or middle-aged patients who may have had excessive sun exposure. It:
  - is locally invasive but almost never metastasizes
  - is best removed by surgical excision with an adequate margin
  - can be treated by radiotherapy, by curettage and cautery, using cryosurgery or with topical imiquimod in certain biopsy-proven tumours.
- **Basal cell carcinomas with a worse prognosis** (high risk) include:
  - large size (>2 cm)
  - central face location: eyes, nose, lips, ears
  - poorly defined clinical margins
  - histological features: morphoeic subtype, perineural or perivascular involvement
  - host immunosuppression
  - recurrence from previous failure of treatment.

The most appropriate treatment for any one tumour depends on its size, site, type and the patient's age. If possible, complete *excision* is the best treatment, as this allows a histological check on the adequacy of removal. If excision is difficult, *radiotherapy* is suitable for those aged ≥60 years. Large tumours around the eye (Fig. 52.6) and the nasolabial fold, especially if of the morphoeic type, are best managed by surgical excision. *Mohs micrographic surgery* (p. 117) may be employed, as the margins of these tumours are often difficult to determine and may be extensive. *Curettage and cautery* is sometimes used for lesions on the trunk or upper extremities. Topical *imiquimod* (also unlicensed 5-fluoruracil) and photodynamic therapy are good treatments for superficial BCCs, but patients need to be pre-warned about the inflammatory reaction and discomfort of the treatment. Cryosurgery is now less widely used but may be useful if repeated topical applications are difficult e.g. on the back (see Table e52.1).

Table e52.1 **Modalities for BCC management**

Modality	Treatable BCC subtype	Body site	Tumour size	Cautions	Advantages	Disadvantages	Ideal candidate	5-year clearance rates (%) in specialist hands
Surgical excision	All (not ideal for superficial, multifocal BCCs)	Any	Usually any	Underlying anatomy may be damaged in high-risk areas, 4–5 mm excision margins recommended to achieve stated clearance rates	Definitive treatment, evidenced by histological analysis	Histological analysis of margins is not 100% reliable	Nodular basal cell carcinoma	95
Mohs micrographic surgery	Any, except superficial	Any, ideal for facial, high-risk lesions	Usually any	Needs to be undertaken by fully trained individuals	Clearance of the lesion confirmed at surgery. Ideal modality for poorly defined, recurrent or large tumours	Prior diagnostic biopsy is recommended. Relatively expensive, time consuming, prolonged procedure	Morphoeic basal cell carcinoma or those near the eye, nose or mouth	99
Curettage and cautery	Any, not usually morphoeic	Non-head and neck not high-risk areas	Ideal for smaller lesions	Need high level of clinical confidence in diagnosis because the histological specimens are fragmented, making assessment more challenging, and often impossible if the lesion is not a BCC	Quick procedures	Can take long periods to heal in the elderly, incomplete treatment	Elderly with large truncal BCC	92
Cryosurgery	Generally only superficial	Body	Smaller lesions	Requires aggressive cryotherapy treatment to be effective, successful treatment depends on careful lesion. No histology to confirm diagnosis	Simple procedure, without requirement for anaesthetic	Painful, may heal slowly	Very infirm individual, unable to tolerate any other modality	>90
Photodynamic therapy	Superficial (curetted nodular lesions)	Flat surfaces	Any	Superficial scale or crust needs removal before treatment	Good cosmetic outcome, multiple lesions can be treated at once	Painful, specialist light source required, time consuming	Multiple superficial BCCs on scalp or shin	86
Imiquimod	Superficial (curetted nodular lesions)	Any	Any	Warn about hypopigmented scars	Non-surgical approach	Requires good patient compliance. Induces painful inflammatory reaction	Multiple superficial BCCs	80
Radiotherapy	Any	Head and neck	Any	Not ideal for bridge of nose, upper eyelid or body sites where skin closely overlies bone, e.g. shin	Non-surgical modality, low medical risk, good cosmesis	Increases risk of malignancy over long term, expensive, frequent attendances required	Elderly with large facial BCC, not tolerant of surgery. Recurrent tumours	91.3

53 Skin cancer – Squamous cell carcinoma

Squamous cell carcinoma (SCC) is a heterogeneous disease comprising clinically distinct but histologically similar entities with differing risk factors implicated in their aetiopathogenesis.

Aetiopathogenesis

SCC is derived from moderately well-differentiated keratinocytes. Ultraviolet (UV) radiation is clearly the strongest predisposing risk factor for this condition. The evidence for this is extensive and includes: a direct correlation between average annual UV radiation and risk of SCC; increased incidence with proximity to the equator; high incidence in albinos versus non-albinos in tropical climates; and an association with the development of features of photoageing such as wrinkles. The increased incidence of SCC in the last 25 years parallels an increased exposure to UVA due to both UVB protective sunscreens, which prevent sunburn but prolong exposure to UVA, and also the increased use of sunbeds.

Predisposing factors include:

- chronic actinic damage, accumulating over a lifetime of sun exposure (p. 102); psoralen with ultraviolet A (PUVA) treatment can predispose
- immunosuppression, e.g. in renal transplant patients (p. 59)
- X-rays or other ionizing radiation; radiant heat (e.g. from a fire; see erythema ab igne, p. 75)
- chronic ulceration and scarring (e.g. a burn, lupus vulgaris or discoid lupus erythematosus, genetic blistering diseases)
- smoking pipes and cigars (relevant for lip lesions)
- industrial carcinogens (e.g. coal tars, oils)
- human papilloma (wart) virus
- genetic factors (e.g. albinos p. 78, xeroderma pigmentosum, p. 97).

Pathology

The malignant keratinocytes, which retain the ability to produce keratin, destroy the dermoepidermal junction and invade the dermis in an irregular manner (Fig. 53.1).

Bowen's disease (in situ squamous cell carcinoma)

Bowen's disease is common and typically occurs on the lower leg in elderly women. The lesions are solitary or multiple. Previous exposure to arsenicals predisposes to the condition.

Pink or lightly pigmented scaly plaques, up to several centimetres in size, are found on the lower leg or trunk. Transformation into invasive SCC is infrequent. Bowen's disease may resemble discoid eczema, psoriasis or superficial basal cell carcinoma. Histologically, the epidermis is thickened and the keratinocytes are atypical, but not invasive. Small biopsy samples may not be representative of the entire lesion and if there is clinical doubt, then larger or excisional biopsies should be undertaken.

Bowen's disease is treated by cryotherapy, curettage, excision, topical 5-fluorouracil or imiquimod or photodynamic therapy (p. 117.e1).

Keratoacanthoma

A keratoacanthoma is a rapidly growing tumour usually arising in the sun-exposed skin of the face or arms (Fig. 53.2). A keratoacanthoma is now generally considered a low-risk SCC, but was previously not regarded as malignant as it may resolve spontaneously, leaving a prominent scar. The tumour grows rapidly over a few weeks into a dome-shaped nodule up to 2 cm in diameter. There is often a keratin plug, which may fall out to leave a crater.

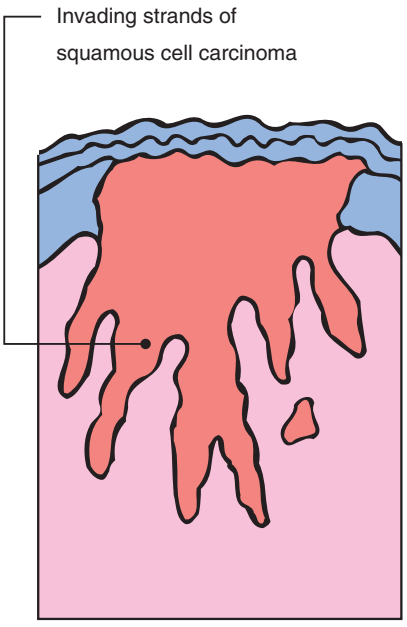


Fig. 53.1 The histological structure of a squamous cell carcinoma.

Histologically, a keratoacanthoma resembles an SCC, although it shows more symmetry and shouldering. Excision is the preferred treatment, but thorough curettage and cautery will usually be satisfactory. If recurrence occurs after curettage, excision is recommended.

Squamous cell carcinoma

SCC is a malignant tumour arising from keratinocytes of the epidermis or hair follicle and is the second most common skin cancer. The incidence of SCC is thought to be approximately a quarter that of basal cell carcinoma (BCC), affecting 2/1000 population per annum. SCC mainly occurs in white-skinned people over 55 years of age, is three times more common in males than in females and may metastasize.

Clinical presentation

SCCs usually develop in sun-exposed sites such as the face, neck, forearm or hand (Fig. 53.3). Commonly, other signs of photodamage will be evident in adjacent skin: solar elastosis, hyperkeratosis, mottled pigmentation and telangiectasia. Premalignant changes such as actinic keratoses and Bowen's disease, as well

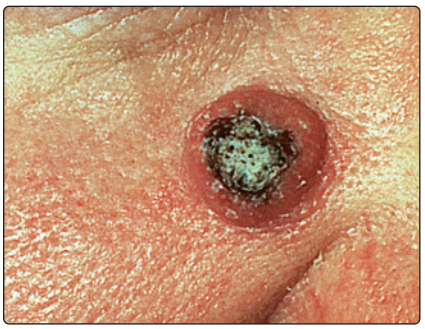


Fig. 53.2 Keratoacanthoma on the face.

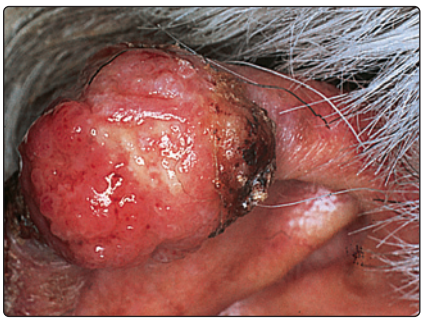


Fig. 53.3 Squamous cell carcinoma. The cancer is seen here on the upper pinna in a patient with actinically damaged skin.

as other skin cancers may also be present. On mucous membranes, leukokeratosis and fissuring or actinic cheilosis are frequent. Lesions present in a variety of ways:

- A hyperkeratotic papule, plaque or cutaneous horn with an indurated base.
- A small ulcer that refuses to heal.
- A firm ulcerated or crusted nodule (Fig. 53.4).
- A friable, fungating tumour that bleeds and weeps.

The tumour may start within an actinic keratosis as a small papule that, if left, progresses to ulcerate and form a crust. This type of SCC does not commonly metastasize. Ulcerating forms of SCC which develop at the edge of ulcers (Fig. 53.5), in scars and at sites of radiation damage are frequently more aggressive. Metastasis is found in 10% or more of these cancers. An important clinical marker of SCC is its rapidity of growth. Most patients will report a lesion that grows over several months (Fig. 53.6), in contrast to a BCC which would frequently develop slowly over 6 or more months. Tenderness is also an important symptom identified in SCCs and is thought to represent the extension of the SCC around nerves.

Differential diagnosis

An SCC needs to be distinguished from keratoacanthoma, actinic keratosis, BCC, in situ SCC (Bowen's disease), amelanotic malignant melanoma and seborrhoeic keratosis. Excisional or incisional biopsy is needed in every case to confirm the diagnosis or adequacy of excision.

Management

Surgical excision is the treatment of choice. Large lesions may require a skin graft. In the elderly, SCCs of the face or scalp can be treated by *radiotherapy* (after an incisional biopsy for histological diagnosis). SCCs can be subdivided into high risk and low risk of recurrence or metastasis, although the exact boundaries are somewhat controversial. Generally agreed features of a high-risk SCC are given in the Box below. Patients are examined for lymph node metastasis at presentation: suspicious nodes are biopsied. Carefully agreed follow-up, especially for high-risk SCCs, is recommended.

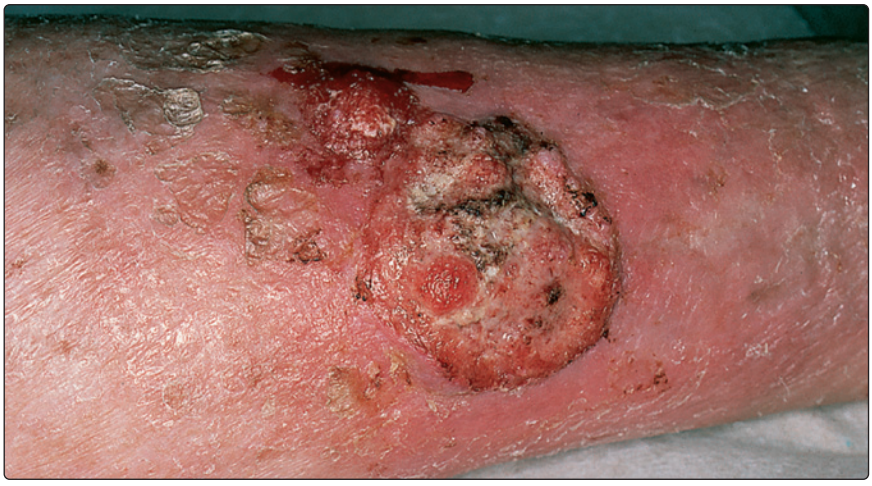


Fig. 53.4 Squamous cell carcinoma on the lower leg. The tumour occurred at the site of a longstanding ulcer.

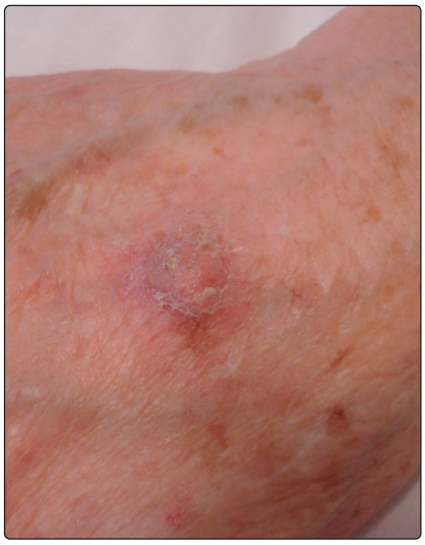


Fig. 53.5 Squamous cell carcinoma on the dorsum of the hand. Adjacent photoageing is evident. Histological examination confirmed that this SCC was 3 mm in thickness.

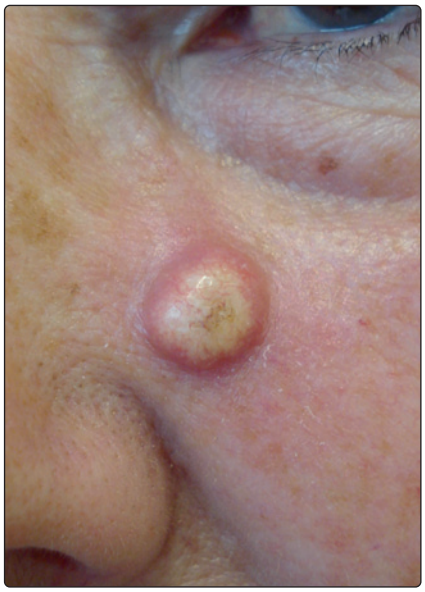


Fig. 53.6 Squamous cell carcinoma on the left cheek. This rapidly growing lesion was firm and tender. Such lesions should be excised urgently and not be managed as a possible cyst.

Squamous cell carcinoma

- **Bowen's disease** is in situ squamous cell carcinoma and follows a less aggressive course. Treatment is with cryotherapy, topical, surgical or photodynamic therapy.
- **Keratoacanthoma** is a spontaneously resolving lesion that bears clinical and histological resemblance to SCC. Excision is recommended.
- **Squamous cell carcinoma** is often seen in the sun-exposed skin of white people in association with signs of actinic damage. A more aggressive form of the tumour is found with chronic scarring. All types are treated by surgical excision.
- **Squamous cell carcinomas with a worse prognosis (high risk) include:**
  - >2 cm in diameter
  - body site involved: lip, ear, non-sun-exposed areas (perineum, sacrum, sole)
  - arising from Bowen's disease, in chronic inflammation (wound/ulcer), or in fields of previous radiotherapy or burns
  - host immunosuppression
  - recurrence from previous failure of treatment
  - histological factors: >4 mm in depth (histologically) or reaching the subcutis (Clark level V), poor differentiation, perineural involvement.

Management of high-risk groups

Severe actinic damage

The combination of fair skin and early life in hot climates, or an outdoor lifestyle increases the risk of squamous cell carcinoma. Individuals will often be freckled and show signs of solar elastosis. Individuals with such extensive damage are best managed with 'field treatment'. This involves topical therapies for actinic keratoses over large areas of sun-damaged skin, with the aim of preventing progression to squamous cell carcinoma.

Immunosuppressed individuals

Transplant recipients, and others treated with immunosuppression need careful advice about photoprotection at the initiation of the immunosuppression. HIV also increases the risk of skin cancer. Avoidance of tanning and burning is essential. Regular, routine screening of such individuals is recommended with the frequency increasing proportional to the length of time on immunosuppression. After 10 years, the risk is high. Ideally, the immunosuppressive medication should be reduced in dose, or stopped if a skin cancer arises. However, in many cases this is not feasible. Particular high-risk drugs are ciclosporin and azathioprine. Methotrexate seems to have a lower risk. Mycophenolate mofetil may offer a slightly lower risk than azathioprine. Low-dose acitretin therapy has been shown to slow the progression of squamous cell carcinomas, and can be useful adjunctive therapy. It is important to note that in immunosuppressed individuals, skin malignancies may have an atypical appearance, often looking more benign, therefore a lower threshold for removal is required.

HPV infection

HPV infection with specific subtypes predisposes to Bowen's disease and invasive SCC. This is more prevalent in immunosuppression (above). HPV vaccines may play a role in preventing this, but to-date, the data regarding cutaneous SCC protection is awaited.

Periungual Bowen's disease may require extensive surgery and or prolonged imiquimod treatment because of the risk of invasive carcinoma.

Novel therapies

BRAF inhibitors for treatment of metastatic melanoma result in the development of squamous cell carcinomas in approximately 25% of cases. This is a direct effect of the molecular pathways that are modified by the drug. It appears that these tumours may have a lower metastatic potential, but nevertheless require treatment. Acitretin has been reported to be beneficial as a preventative therapy.

Genetic syndromes

Xeroderma pigmentosum (and variants), oculocutaneous albinism and epidermodysplasia verruciformis are rare inherited conditions, giving rise to an increased risk of skin cancer. Strict sun avoidance for life is the best approach to management.

54 Skin cancer – Malignant melanoma

Malignant melanoma is a malignant tumour of melanocytes, usually arising in the epidermis. It is the most lethal of the main skin tumours and has increased almost sevenfold in incidence since the 1970s, but overall there is 90% survival at 5 years. The important pathogenic role of excessive ultraviolet (UV) radiation exposure is estimated to contribute to 86% of cases and has been the subject of public education campaigns. Genetics may be important, and up to 5% of patients have a family history of malignant melanoma.

Clinical presentation

Four main clinicopathological variants are recognized.

Superficial spreading malignant melanoma

This type accounts for 50% of all British cases, shows a female preponderance and is commonest on the lower leg. The tumour is macular and shows variable pigmentation, often with regression (Fig. 54.1).

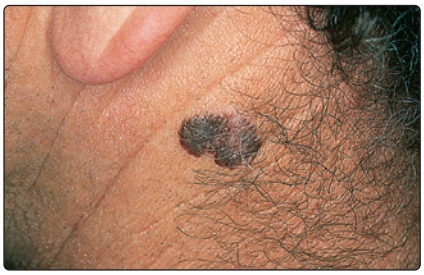


Fig. 54.1 Superficial spreading malignant melanoma.

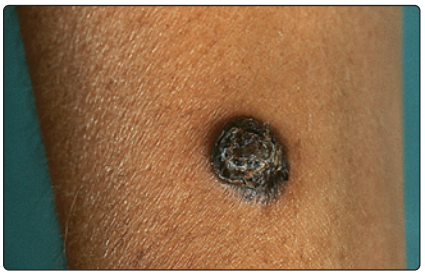


Fig. 54.4 Nodular malignant melanoma.

Lentigo malignant melanoma

Malignant melanoma developing in a longstanding lentigo maligna (Fig. 54.2) constitutes 15% of UK cases. A lentigo maligna arises in sun-damaged skin, often on the face of an elderly person who has spent many years in an outdoor occupation.

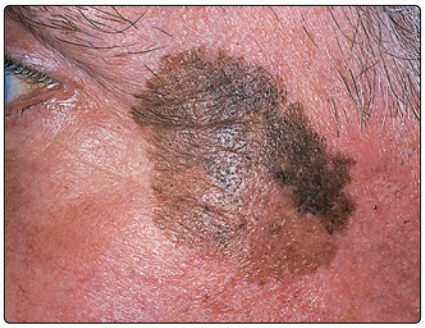


Fig. 54.2 Lentigo maligna showing irregular outline and pigmentation.

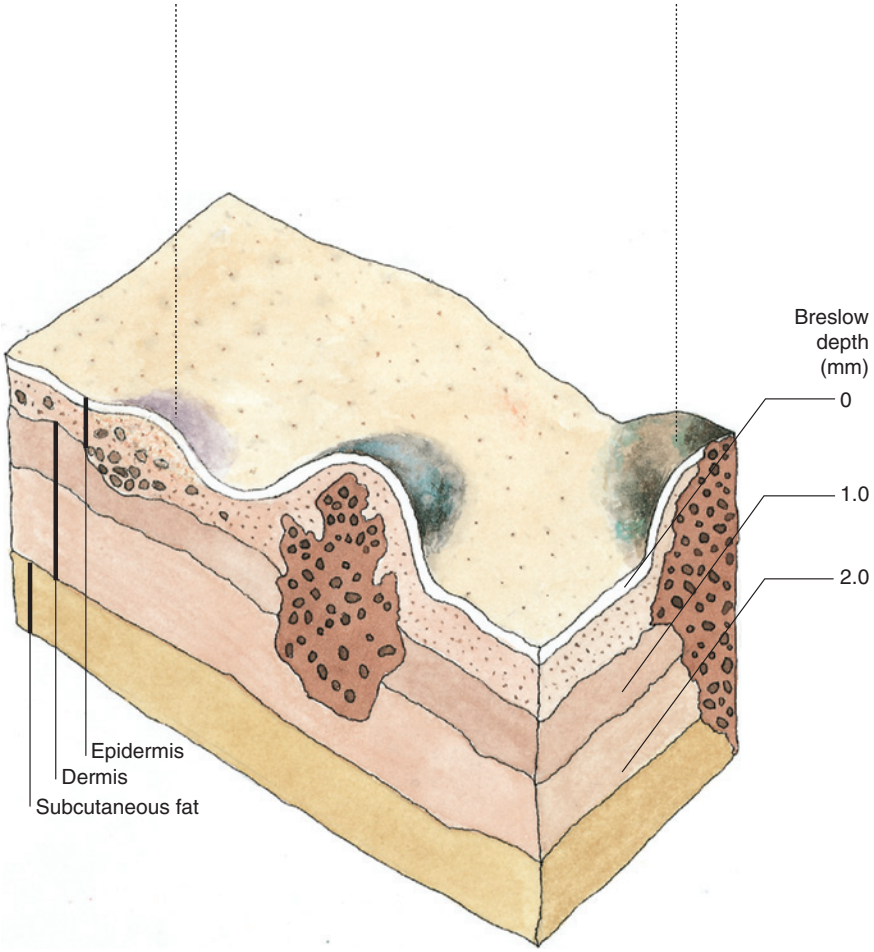


Fig. 54.5 Micro-staging by Breslow thickness (distance from epidermal granular layer to deepest tumour cell) determines prognosis.

Acral lentiginous malignant melanoma

The acral lentiginous type makes up 1 in 10 of British cases, but is the commonest form in dark-skinned races. The tumour affects the palms, soles (Fig. 54.3) and nail beds, is often diagnosed late and has poor survival figures.

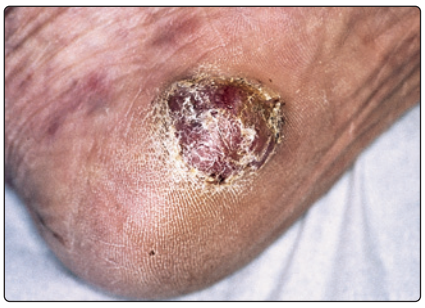


Fig. 54.3 Acral lentiginous malignant melanoma.

Nodular malignant melanoma

The nodular variant is seen in 25% of British patients; it shows a male preponderance and is commonest on the trunk. The pigmented nodule (Fig. 54.4) may grow rapidly and ulcerate.

The *differential diagnosis* of malignant melanoma includes:

- benign melanocytic naevus (p. 100)
- seborrhoeic wart (p. 98)
- haemangioma (p. 99)
- dermatofibroma (p. 98)
- pigmented basal cell carcinoma
- benign lentigo (p. 79).

Epidemiology

Malignant melanoma has an incidence in the UK of 21.1 per 100 000 population per year. Over the last decade, incidence rates in the UK have risen 57% and 39% in males and females, respectively. Superficial spreading and nodular

melanomas tend to occur in those in the 20–60-year age group, whereas lentigo malignant melanomas mostly affect those over 60 years old. In males, the commonest site is the back; in females, it is the lower leg (about half occur here).

Staging

Malignant melanomas usually progress through two phases: *horizontal* growth in the epidermis then *vertical* invasion of the dermis (Fig. 54.5).

Local invasion by the tumour is assessed using the *Breslow method*, which is the measurement in millimetres of the distance between the granular cell layer to the deepest identifiable melanoma cell. Histological ulceration is also important. Metastasis is uncommon in tumours restricted to the epidermis.

Aetiopathogenesis

The main risk factor that increases risk of melanoma is exposure to UV radiation. Some people are more at risk of melanoma than others (Fig. 54.6). Histological evidence of a pre-existing melanocytic naevus is found in 30% of malignant melanomas but, with the exception of dysplastic or congenital naevi, the risk of change in a common melanocytic naevus is small.

Diagnosis

Any of the following changes in a naevus or pigmented lesion may suggest malignant melanoma:

- *Area/size*: usually a recent increase
- *Border/shape*: irregular in outline
- *Colour*: variation, darker or lighter
- *Diameter*: usually >5 mm
- *Evolution: recent history of change (over 3–6 months)*
- *Other features to note*: **inflammation** may be at the edge, **crusting** or **ooze** or **bleeding**, **itching** is uncommon.

Pigmented lesions referred from primary care should be evaluated by dermoscopic examination.

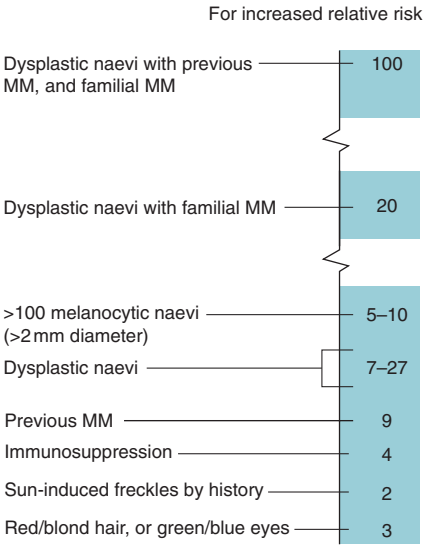


Fig. 54.6 Major risk factors. The major risk factors and their relative risk for the development of malignant melanoma (MM) are shown. *(Data derived from Psaty EL, Scope A, Halpern AC, Marghoob AA. 2010. Int J Dermatol 49:362–376.)*

Prognosis

The prognosis relates to the tumour depth. The approximate 5-year survival rates are:

- <1 mm (95%)
- 1.01–2 mm (90%)
- 2.01–4 mm (77%)
- >4 mm (65%)

Histological ulceration, lowers the 5-year survival by approximately 10%. Examples of thin and thick tumours are given in Figs 54.7 and 54.8.

Management

The primary treatment is narrow surgical excision followed by re-excision of the scar dependent upon Breslow thickness. In situ tumours require a 0.5-cm re-excision, those up to 1 mm thick require a 1-cm margin, those of 1–2 mm thickness need a 2-cm margin and thicker tumours require a 2–3-cm clearance. A skin graft may be necessary to close the defect. Regular follow-up is needed to detect any recurrence, of which there are three main types:

1. *Local* (Fig. 54.9)
2. *Lymphatic* – either in the regional lymph nodes or in transit in the lymphatics draining from the tumour to the nodes
3. *Blood-borne* to distant sites.

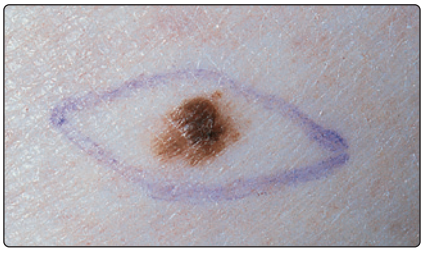


Fig. 54.7 A thin (0.8-mm Breslow thickness) superficial spreading malignant melanoma with a good prognosis.

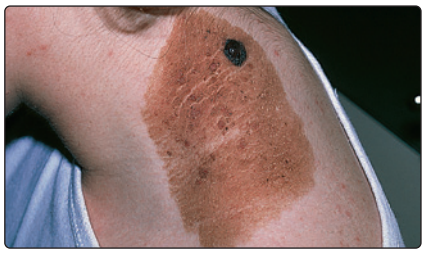


Fig. 54.8 A thick (11-mm Breslow thickness) nodular malignant melanoma developing within a large congenital naevus. Local lymph nodes were involved; the prognosis was poor.

Sentinel node biopsy should be offered to those with melanomas with Breslow thickness >1 mm. Positive nodes infer poorer prognosis and elective lymph node dissection may be considered. For advanced metastatic disease, radiotherapy is of limited use and standard chemotherapy provides minimal survival advantage. New therapies based around genetic testing of the tumour for mutations in BRAF (V600 mutation in approx. 50% of melanomas) include BRAF kinase inhibitors (e.g. dabrafenib, vemurafenib), often with MAPK kinase inhibition (trametinib), and show benefit. Monoclonal antibodies targeting the negative T cell regulator molecules, CTLA-4 (ipilimumab) and PD1 (nivolumab, lambrolizumab), separately or combined, also show exciting promise but frequent adverse events.

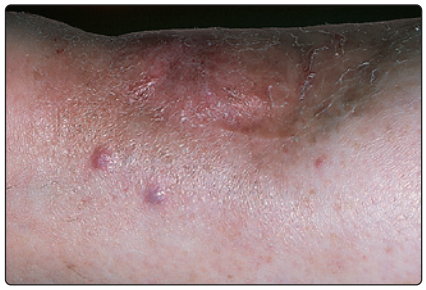


Fig. 54.9 Hypomelanotic recurrent malignant melanoma. Pink papules of recurrent tumour are evident at the edge of a previously excised and grafted site.

Prevention and public education

Early malignant melanoma is a curable disease, but thick lesions have a poor prognosis. Public health education should encourage early visits to the doctor for changing pigmented lesions and should discourage excessive sun exposure, especially in fair-skinned individuals or those with numerous melanocytic naevi. The best advice is:

- Avoid burning in the sun
- Report early any change in a mole.

Malignant melanoma

- The UK incidence is 21.1 per 100 000 per year.
- The female to male ratio is 2:1.
- The incidence has risen by 7% per year and doubled in the past two decades.
- The incidence is proportional to the geographical latitude, suggesting an effect of ultraviolet radiation.
- The prognosis is related to tumour thickness. Early lesions are curable by surgical excision.
- New treatments for metastatic melanoma show promise but can cause severe adverse events.

Further reading – online sources

More information on melanoma for professionals can be found at the Cancer Research UK website (access via http://www.cancerresearchuk.org/) and the National Cancer Institute (access via http://www.cancer.gov/types/skin/hp).

Further reading – textbooks

There are many textbooks devoted to skin cancer management. Pre-malignant diseases are best reviewed in standard texts:

Bolognia, J.L., Jorizzo, J.L., Schaffer, J.V. (Eds.), 2012. Dermatology, third ed. Elsevier Saunders, Philadelphia.

Griffiths, C., Barker, J., Bleiker, T., Chalmers, R., Creamer, D. (Eds.), 2016. Textbook of Dermatology, ninth ed. Wiley-Blackwell, Oxford.

55 Cutaneous T cell lymphomas and malignant dermal tumours

Cutaneous T cell lymphoma (CTCL) is the most common type of skin lymphoma, with an incidence of 0.6 per 100,000. B cell lymphoma of the skin is rare. Malignant tumours of the dermis are infrequent. The commonest are secondary deposits (p. 92), Kaposi's sarcoma (p. 58) and a malignancy of dermal fibroblasts (dermatofibrosarcoma).

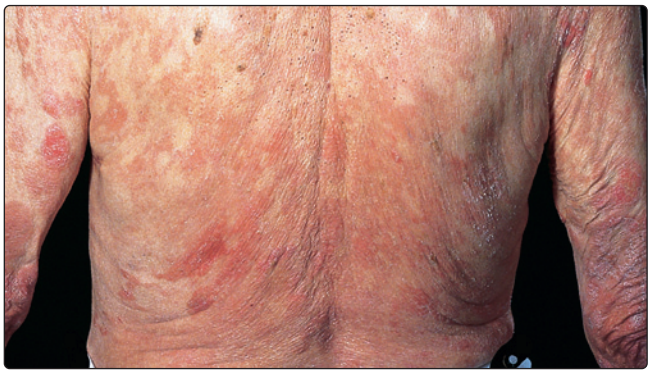


Fig. 55.2 CTCL showing infiltrated plaques on the back and arms.

Cutaneous T cell lymphoma (mycosis fungoides)

CTCL describes a lymphoma that evolves in the skin, although extracutaneous T cell tumours often produce secondary skin deposits. CTCL is a slowly progressive tumour of epidermotropic CD3+, CD4+ T lymphocytes that becomes systemic only in its terminal stage.

Clinical presentation

The course is usually protracted, although it is occasionally more rapidly progressive. The diagnosis is often delayed for some years as, in its initial stages, CTCL may resemble eczema or 'chronic superficial dermatitis' (p. 44). CTCL can be regarded as having four stages:

1. *Patch stage*. Describes small, scaly, slightly raised erythematous patches, typically on the trunk, that can resemble eczema (Fig. 55.1). It may persist for ≥10 years. Occasionally, the skin becomes atrophic, pigmented and telangiectatic (poikiloderma).
2. *Infiltrated plaques*. Fixed plaques develop, usually on the trunk but sometimes more widely distributed (Fig. 55.2). This stage may last for years.

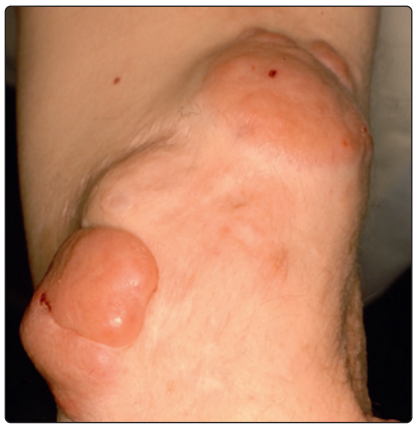


Fig. 55.3 Tumour stage of CTCL.

3. *Tumour stage*. This later phase, characterized by tumorous nodules or ulcers within the plaques, has a 5-year survival of 40–65% (Fig. 55.3).
4. *Systemic disease*. Involvement of lymph nodes or internal organs is a late finding. The Sézary syndrome (p. 46) is a variant.

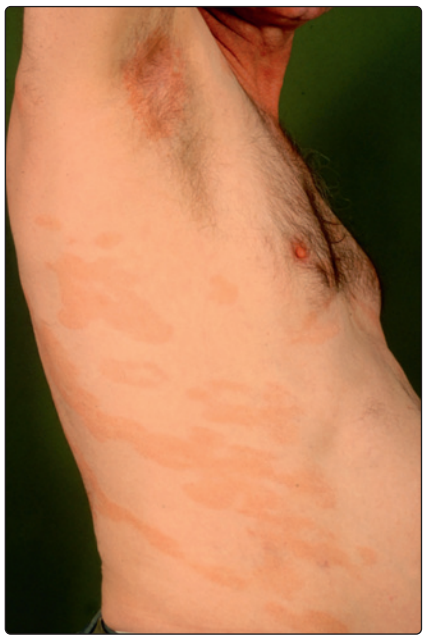


Fig. 55.1 Patch stage CTCL on trunk.

Differential diagnosis

Chronic superficial dermatitis, undifferentiated eczema and psoriasis are the main differential diagnoses. Those cases of chronic superficial dermatitis that show larger patches are said to be more likely to progress to CTCL. CD30+ lymphoproliferative disorders represent a subgroup of skin lymphomas. They present either as multiple nodules that heal with scarring and follow a protracted course (lymphomatoid papulosis) or as large cell lymphoma, in which ulcerated nodules appear on the trunk.

Management

Diagnosis relies on matching the clinical and pathological appearances. T cell receptor gene analysis demonstrates clonality of the lymphocytic infiltrate. Current treatment is not curative but aimed at controlling the lymphoma. The patch-stage lesions often improve with moderately potent topical steroids and ultraviolet (UV) B therapy. More infiltrated plaques require PUVA or topical nitrogen mustard. Localized lesions respond to conventional radiotherapy. Advanced CTCL can be treated with extracorporal photopheresis (p. 113), electron beam therapy, oral bexarotene or combined chemotherapy.

Cutaneous T cell lymphomas and malignant dermal tumours

- **Definition:** CTCL is an uncommon tumour resulting from infiltration of the skin by malignant clonal CD3+, CD4+ T lymphocytes.
- **Stages:** CTCL progresses through the patch stage to indurated plaques, and then to tumours and systemic involvement.
- **Treatment:** therapy depends on the stage and extent of the disease. Localized patch stage CTCL responds to topical steroids and phototherapy. In more advanced disease, phototherapy, radiotherapy and oral bexarotene or chemotherapy may be prescribed.
- **Malignant dermal tumours** are uncommon. Secondary deposits, Kaposi's sarcoma and other sarcomas can be found.

Staging of cutaneous T cell lymphoma

At presentation, it is important for the medical team to correctly stage the patient's cutaneous T cell lymphoma. Broadly, there are slow growing types such as classical mycosis fungoides or primary cutaneous CD30-positive lymphoproliferative disorders such as lymphomatoid papulosis, and faster growing types such as Sézary syndrome or adult T cell leukaemia/lymphoma. The Lymphoma Association gives clear information on some aspects of further management (access via https://www.lymphomas.org.uk/). It is also useful to review the classification of the European Organisation for the Treatment of Cancer (EORTC) (accessed via http://www.eortc.org/).

The management of CTCL requires a multidisciplinary team approach and often the use of combined therapeutic modalities. An indication of how treatment is tailored can be found on the MedScape website (accessed via http://emedicine.medscape.com/).

Lymphomatoid papulosis

Lymphomatoid papulosis is one of the lymphoproliferative disorders (along with primary cutaneous anaplastic CD30+ large cell lymphoma and subcutaneous panniculitis-like T cell lymphoma). It is characterized by recurrent crops of papules or nodules that occur in crops often on the trunk and developing over the period of a few days (Fig. e55.1). They are often necrotic and heal over 1–3 months, to leave an atrophic circular scar. Histologically, the cutaneous lymphocytic infiltrate includes CD30+ cells. Treatment is with various types of phototherapy and low-dose oral methotrexate. The condition is recurrent over several years. A small number of patients develop a more progressive lymphoma.

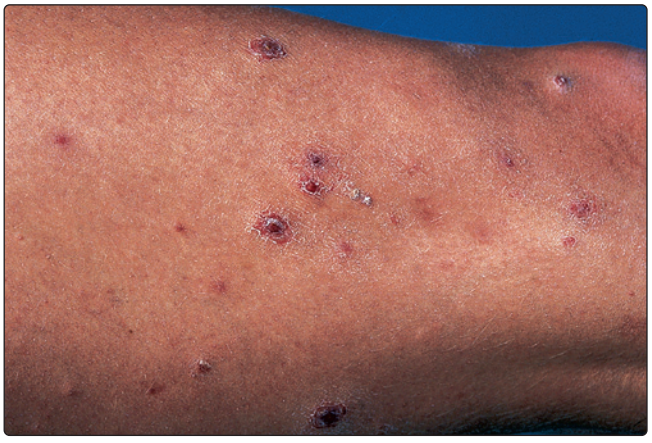


Fig. e55.1 Lymphomatoid papulosis. Scattered papules are seen, some of which are necrotic. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Primary cutaneous B cell lymphoma

Primary B cell lymphomas of the skin are less common than the T cell type (Fig. e55.2). Most are indolent, e.g. marginal zone lymphoma and follicle centre cell lymphoma, and have a good long-term prognosis. Superficial radiotherapy is often the treatment of choice. Further information is available in specialized texts.

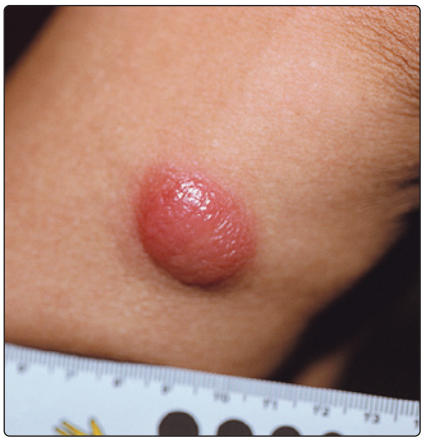


Fig. e55.2 Cutaneous B cell lymphoma. Presenting as an erythematous dermal nodule. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Primary skin tumours of dermal origin

Sarcomas and other tumours of the skin are uncommon. *Dermatofibrosarcoma protuberans* has an incidence of 4 per million (per year). It is a locally invasive tumour that presents often on the trunk, flexures or proximal limbs as a painless flesh-coloured dermal nodule (Fig. e55.3). Usually a dermatofibrosarcoma enlarges slowly. Palpation reveals a hard indurated plaque with an irregular outline. Wide excision is required to prevent local recurrence.

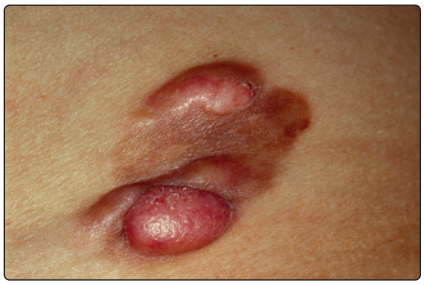


Fig. e55.3 Recurrent dermatofibrosarcoma protuberans. Plum-coloured dermal nodules are evident. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Further reading – online sources

For classification, readers are referred to the European Organisation for the Treatment of Cancer (EORTC) (access via http://www.eortc.org//). Management is discussed on the emedicine website (access via http://emedicine.medscape.com/) and the Lymphoma Association website (access via https://www.lymphomas.org.uk/).

Further reading – textbooks

Rigel, P.S., Robinson, J.K., Ross, M., et al., 2011. Cancer of the Skin, second ed. WB Saunders, Philadelphia, PA.

3

Special Topics in Dermatology

56 Phototherapy

An interaction between natural sunlight and the skin is inescapable. The potential for harm depends on the type and length of exposure. Sunlight can help in certain skin diseases (p. 49). Both ultraviolet (UV)B and UVA are extensively used therapeutically. UVA is usually used combined with photosensitizing psoralens given systemically or topically, although by itself it has some therapeutic effects. Photoageing is a growing problem (p. 123), because of an increasingly aged population and a rise in the average individual exposure to ultraviolet (UV) radiation.

The sun's radiation spectrum

The sun's emission of electromagnetic radiation ranges from low-wavelength ionizing cosmic, gamma and X-rays to the non-ionizing UV, visible and infrared higher wavelengths (Fig. 56.1). The ozone layer absorbs UVC, but UVA and smaller amounts of UVB reach ground level. UV radiation is maximal in the middle of the day (11.00–15.00 h) and is increased by reflection from snow, water and sand. UVA penetrates the epidermis to reach the dermis. UVB is mostly absorbed by the stratum corneum – only 10% reaches the dermis. Most window glass absorbs UV <320 nm in wavelength. Artificial UV sources emit in the UVB or UVA spectrum. Sunbeds largely emit UVA.

Effects of light on normal skin

Physiological

UVB promotes the synthesis of vitamin D3 from its precursors in the skin, and UVA and UVB stimulate immediate pigmentation (due to photo-oxidation of melanin precursors), melanogenesis and epidermal thickening as a protective measure against UV damage (p. 7).

Sunburn

If enough UVB is given, erythema always results. The threshold dose of UVB – the *minimal erythema dose* (MED) – is a guide to an individual's susceptibility. Excessive UVB exposure results in tingling of the skin, followed 2–12 h later by erythema. The redness is maximal at 24 h and fades over the next 2 or 3 days to leave desquamation and pigmentation. Severe sunburn causes oedema, pain, blistering and systemic upset. The early use of topical steroids may help sunburn; otherwise, a soothing shake lotion (e.g. calamine lotion) is applied. Individuals may be skin typed by their likelihood of burning in the sun (Table 56.1). Prevention is better than cure, and 'Celts' with a fair 'type 1' skin should not sunbathe and must use a high protection factor sunblock cream on exposed sites (p. 118). Some evidence suggests the sun avoidance message may have gone too far, in that it could be causing some people to become vitamin D deficient.

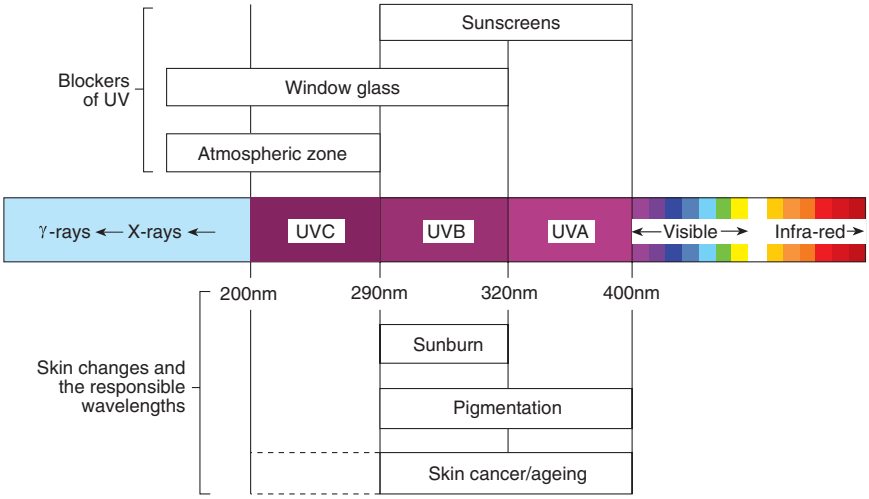


Fig. 56.1 The sun's emission spectrum.

Table 56.1 **Skin type according to sunburn and suntan histories**

Skin type	Reaction to sun exposure
Type 1	Always burns, never tans
Type 2	Always burns, sometimes tans
Type 3	Sometimes burns, always tans
Type 4	Never burns, always tans
Type 5	Brown skin (e.g. Asian caucasoid)
Type 6	Black skin (e.g. black African)

Treatments

Phototherapy with ultraviolet B

UVB has several effects in the skin including the release of prostaglandins and cytokines (e.g. IL-1 and IL-6), suppression of DNA synthesis and effects on extranuclear molecular targets. UVB (290–320 nm) is given three times a week. The starting dose is decided from the patient's MED or skin type. The dosage is increased on each visit according to a schedule. A course of 10–30 treatments is usual. Narrow-band (311 ± 2 nm: TL01) UV lamps are superior to broadband and allow a lower dose of UV to be used.

UVB is used to treat psoriasis and mycosis fungoides and, occasionally, atopic eczema, vitiligo and pityriasis rosea. It can be given to children and women during pregnancy. Its main side-effects are acute sunburn and an increased long-term risk of skin cancer. Some units that serve large geographic areas offer self-treatment using home-based UV cabinets, supervised by specialist nurses.

When used to treat psoriasis, UVB may be combined with a topical preparation such as a vitamin D analogue (p. 22), tar or dithranol, or with oral acitretin.

Photochemotherapy (PUVA)

In psoralen plus UVA (PUVA) therapy, 8-methoxypsoralen (MOP), taken orally 2 h before UVA (320–400 nm) exposure (Fig. 56.2), is photoactivated. This causes

Fig. 56.2 Photochemotherapy using UVA-emitting tubes.

UVB has several effects in the skin including the release of prostaglandins and cytokines (e.g. IL-1 and IL-6), suppression of DNA synthesis and effects on extranuclear molecular targets. UVB (290–320 nm) is given three times a week. The starting dose is decided from the patient's MED or skin type. The dosage is increased on each visit according to a schedule. A course of 10–30 treatments is usual. Narrow-band (311 ± 2 nm: TL01) UV lamps are superior to broadband and allow a lower dose of UV to be used (Fig. e56.1).

Useful practical guidance on how to conduct phototherapies of various types can be obtained from the website of Ninewells Hospital, Dundee, Scotland, UK (see 'Tayside documents', access via http://www.nhstayside.scot.nhs.uk/index.htm).

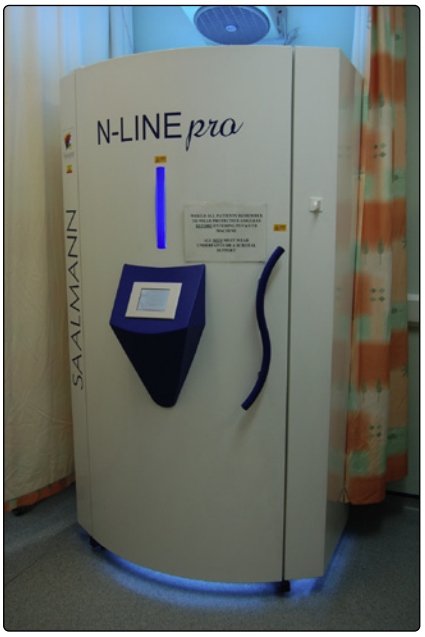


Fig. e56.1 A narrow-band (TL01) phototherapy cabinet.

cross-linkage in DNA, inhibits cell division and suppresses cell-mediated immunity. PUVA is usually given for psoriasis or mycosis fungoides, and sometimes for atopic eczema, polymorphic light eruption (p. 48) or vitiligo (p. 78). The initial dose of UVA is determined by the minimum toxic dose (the MED for PUVA) or skin type, and is increased according to a schedule. PUVA is given two or three times a week and leads to clearance of psoriasis (with tanning) in 15–25 treatments. Maintenance PUVA is not recommended. PUVA can be combined with acitretin ('Re-PUVA') and over the short-term, with methotrexate, but it should not be given with ciclosporin (because of enhanced carcinogenicity).

The immediate side-effects of pruritus, nausea and erythema are usually mild. The long-term risks of skin cancer and premature skin ageing are related to the number of treatments or total UVA dose. Careful records must be kept. Cataracts are theoretically possible, and UVA-opaque sunglasses must be worn for 24 h after taking the psoralen. In patients who have excessive nausea with 8-MOP, 5-MOP is an alternative although the UVA doses required for clearance are higher.

Bath PUVA, in which the patient soaks in a bath containing a psoralen, is an alternative, especially if systemic side-effects make the oral route impractical. A lower dose of UVA is needed. *Local PUVA* using topical psoralen is useful for psoriasis or dermatitis of the hands or feet.

Phototherapy with UVA-1

UVA-2 (320–340 nm) resembles UVB in its ability to induce erythema. UVA-1 (340–400 nm) is less erythemogenic and penetrates deeper into the dermis. It has been used in some centres to treat atopic eczema, localized scleroderma (p. 85), mycosis fungoides and urticarial pigmentosa (p. 120). UVA-1 may be as effective as narrow-band UVB in atopic eczema. Side-effects are fewer than with UVB. UVA-1 is given five times per week for 3–4 weeks. The therapeutic benefit may be due to induction of T cell apoptosis, reducing Langerhans cell and mast cell numbers, and enhancing collagenase expression.

Targeted phototherapy

Targeted phototherapy may be given with the 308 nm Excimer laser or light source in patients with psoriasis, vitiligo and mycosis fungoides (Fig. 56.3). As the 'spot size' is only 2 cm^2 the treatment is suitable for localized areas of disease such as in psoriasis, palms, soles, elbows or knees, in vitiligo, areas on the face or hands, or single lesions of mycosis fungoides.

Fig. 56.3 The Excimer 308 nm laser. It can be used for treating localized areas of psoriasis, vitiligo or mycosis fungoides.

Photopheresis

Photopheresis (extracorporal photochemotherapy) is a specialized treatment for the Sézary syndrome (p. 46) and some forms of graft-versus-host disease (p. 87). After the patient has taken oral 8-MOP, blood is taken continuously from a vein, passed through a flow cell separator where mononuclear cells are harvested, exposed to UVA and then re-infused along with the red cells. The process is thought to induce regulatory T cells. The treatment is typically given on two successive days every 2–4 weeks.

Prophylaxis of photodermatoses

Low-dose photo(chemo)therapy with both UVB (broad-band or TL01) and PUVA has been used to induce tolerance in various photodermatoses including polymorphic light eruption, solar urticarial and chronic actinic dermatitis (p. 48).

Sunbeds

Sunbeds emit UVA radiation and have been used by 10–20% of adults in the UK. They will produce a tan in people with skin types 3 and over, but those with type 1 and 2 skin will not tan so well, if at all. Side-effects, particularly redness, itching and dry skin, are seen in half of all users. More serious effects can occur in patients taking drugs or applying preparations with a photosensitizing potential. An acute photosensitive eruption may develop, and intense pigmentation sometimes follows. Sunbeds can exacerbate polymorphic light eruption and systemic lupus erythematosus, and may induce porphyria-like skin fragility and blistering. They are a weak risk factor for malignant melanoma, and may cause premature skin ageing.

Dermatologists discourage sunbed use, particularly in the fair-skinned, in those with several melanocytic naevi and in anyone with a history of skin cancer. Patients who, despite these warnings, wish to use a sunbed should not do so more than twice a year and should limit each course to 10 sessions. Sunbeds are not recommended for the treatment of skin disease.

Phototherapy

- **UVB radiation** is mostly absorbed by the epidermis, but UVA can penetrate to the dermis. UVB promotes vitamin D synthesis. UVA and UVB stimulate melanogenesis and epidermal thickening.
- **Minimal erythema dose** is the threshold amount of UVB to cause erythema.
- **UVB therapy**, now mostly narrowband TL01, is mainly used in psoriasis; a course of 10–30 treatments is usual.
- **PUVA** has been a common treatment for psoriasis; used less now. Skin cancer is one potential long-term sequela.
- **UVA-1 therapy** may be used for atopic eczema, localized scleroderma and urticaria pigmentosa.
- **Targeted phototherapy** with the 308 nm Excimer laser may be helpful for localized psoriasis, vitiligo and mycosis fungicides.
- **Sunburn** is maximal at 24 h and fades at 2–3 days to leave desquamation and pigmentation of the skin.
- **Sunbeds** emit UVA and will induce a tan in those with type 3 or 4 skin. Side-effects are common.

Bath PUVA, in which the patient soaks in a bath containing a psoralen, is an alternative, especially if systemic side-effects make the oral route impractical. A lower dose of UVA is needed. *Local PUVA* using topical psoralen is useful for psoriasis or dermatitis of the hands or feet (Fig. e56.2).

Photoageing

Photoageing describes the skin changes resulting from chronic sun exposure. Photoaged skin is coarse, wrinkled, pale-yellow in colour, telangiectatic, irregularly pigmented, prone to purpura and subject to benign and malignant neoplasms (Fig. e56.3). Some of these changes resemble those of intrinsic ageing, but the two are not identical, as may be judged by comparing, in an elderly patient, the sun-exposed face with the sun-protected buttock. The features of photoageing are usually more striking, particularly the development of premalignant and malignant tumours. Some rare conditions, e.g. xeroderma pigmentosum (p. 97), predispose to photoageing.

Histologically, the photoaged dermis shows tangled clumps of elastin with proliferation of glycosaminoglycans (Fig. e56.4). The epidermis is variable in thickness, with areas of atrophy and hypertrophy and a variation in the degree of pigmentation. *In vitro*, keratinocytes and fibroblasts from sun-exposed sites have a reduced proliferative ability compared with cells from sun-protected sites. The specific clinical changes of photoageing are discussed on page 123.

Management of photoageing

Prevention is the most effective treatment and is particularly important for those with fair (type 1 or 2) skin. Avoidance of prolonged, direct sun exposure by wearing long-sleeved shirts and a wide-brimmed hat is useful, and sunscreens (p. 118) are applied to sites that are likely to receive some sun, such as the face and hands. The use of tretinoin or alpha hydroxy acids, in cream formulations, has been shown partially to reverse the clinical and histological changes of photoageing. Chemical peels and laser resurfacing are also used.

Fig. e56.2 A UVA phototherapy machine for treating the hands and the feet.

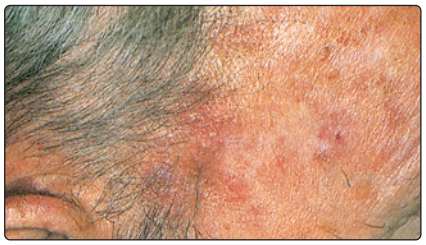


Fig. e56.3 Photoageing of the skin. Keratoses and pigmentation are evident.

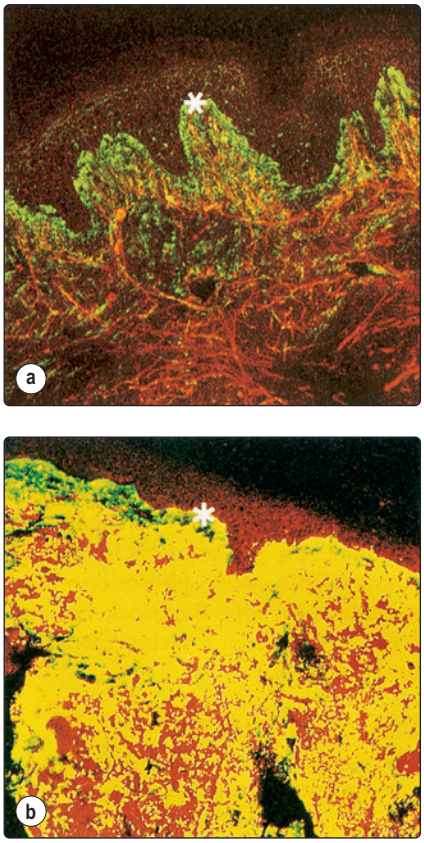


Fig. e56.4 (a) Sun-protected skin. Preservation of the normal pattern of glycosaminoglycan (GAG: green, hyaluronan) and fibriform elastin (red) is shown. (*) shows the dermoepidermal junction (DEJ). **(b) Sun-exposed elastotic skin.** Tangled clumps of elastin (red) are shown, with proliferations of GAG (chondroitin sulphate) co-localized to elastin (yellow) throughout the dermis. (*) shows the DEJ. *(Courtesy of the British Journal of Dermatology and Dr E.F. Bernstein of Jefferson Medical College, Philadelphia, PA, USA.)*

- **Photoageing** describes coarse, wrinkled, yellowed skin, prone to tumours, resulting from excess sun exposure.
- **Treatment of photoageing:** prevention is best, but tretinoin cream can reverse some of the changes.

Further reading – online sources

More information on ultraviolet radiation can be found at the Medscape website (access via http://emedicine.medscape.com).

For practical guidance on phototherapies, see the website of Ninewells Hospital, Dundee, Scotland, UK (search under 'NHS Tayside documents', access via http://www.nhstayside.scot.nhs.uk/index.htm).

Further reading – textbooks

Ultraviolet radiation effects on the skin are best reviewed in standard texts:

Bolognia, J.L., Jorizzo, J.L., Schaffer, J.V. (Eds.), 2012. Dermatology, third ed. Elsevier Saunders, Philadelphia.

Griffiths, C., Barker, J., Bleiker, T., Chalmers, R., Creamer, D. (Eds.), 2016. Textbook of Dermatology, ninth ed. Wiley-Blackwell, Oxford.

Gilchrest, B.A., Krutmann, J. (Eds.), 2006. Skin Aging. Springer, Berlin.

Zanolli, M.D., Feldman, S., 2005. Phototherapy Treatment Protocols for Psoriasis and Other Skin Diseases, second ed. Taylor & Francis, London.

57 Basic dermatological surgery

The demand for the removal of benign and malignant skin lesions has increased considerably, such that skin surgery is now practised by many general practitioners as well as by dermatologists. Knowledge of basic surgical techniques is mandatory for all those who treat skin disease.

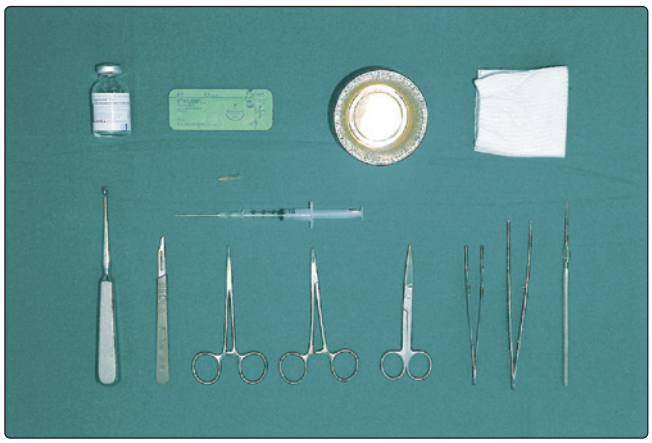


Fig. 57.1 A typical surgical set for skin surgery. A curette is included.

Instruments and methods

No one should attempt a procedure if unsure about it. Those with limited experience should remove only benign lesions. All procedures are ideally performed in an *operating theatre* with trained nurses and adequate lighting. Sterile instruments, an aseptic technique and sterile gloves are essential. The operator plans the procedure, explains it to the patient, discusses the scar and obtains written consent. The direction of crease marks is assessed: any excision is usually made parallel to these lines.

The *basic instruments* (Fig. 57.1) include a No. 3 scalpel handle and No. 15 blade, a toothed Adson's forceps, a small smooth-jawed needle holder, a pair of fine scissors, artery forceps and a Gillies skin hook. Curettes and skin punches come in various sizes. A solution of 1% lidocaine (Xylocaine) with 1/200 000 adrenaline (epinephrine) is usually satisfactory as the *local anaesthetic*, but plain lidocaine is preferred on the fingers, toes and penis. The maximum safe dose for an 80-kg person using 1% lidocaine and adrenaline (1/200 000) is 40–50 mL. This volume is significantly reduced if higher concentrations of lidocaine or no adrenaline are used. The skin is prepared (but not sterilized) using, for example, 0.05% aqueous chlorhexidine (Unisept). Alcohol-based preparations are avoided as, if cautery is used, the solution may ignite. Sterile towels, placed around the operation site, reduce the chance of infection.

Absorbable subcutaneous sutures (e.g. polyglactin; Vicryl) are used for excisions where the wound may be deep or under tension. For cuticular stitches, monofilament nylon (e.g. Ethilon) and polypropylene (e.g. Prolene) are recommended. Use 5/0 or 6/0 sutures on the face, 3/0 on the back and legs, and 4/0 elsewhere. Stitches are preferably removed at 5–7 days on the face, 10–14 days on the legs or trunk and 7–8 days at other sites. Steristrips give extra support to a wound either in addition to sutures or when applied after their removal. An adherent tape or dressing (e.g. Micropore or Mepore) is used in most cases. For scalp biopsies, spray adhesive (e.g. Opsite spray) is useful.

Every biopsied lesion is sent for histology. If more than one specimen is taken from a patient, separate pots are used and each labelled before the biopsy is placed in it. The usual fixative is 10% formalin.

Basic surgical techniques

Excisional biopsy

An excisional biopsy is planned after considering the local anatomy. The excision's axis depends on the skin creases (Fig. 57.2) and its margin on the nature of the lesion. The ellipse to be excised is drawn on the skin using a marker pen. An ellipse has an apical angle of about 30° and is usually three times as long as it is wide. If any shorter, then 'dog-ears' appear at either end, although these can easily be corrected. After cleaning, local anaesthetic is infiltrated using a fine needle into the area of the lesion. Once numbed, the skin is incised vertically down to fat with the scalpel, in a smooth continuous manner to complete both arcs of the ellipse. The ellipse is freed from surrounding skin, secured at one end with a skin hook and removed from the underlying fat, usually using the scalpel blade (Fig. 57.3). In most cases, the wound can now be repaired, although any bleeding vessels will need to be stemmed with cautery, hyfrecation or suturing.

In a simple *interrupted skin suture*, the needle is inserted vertically through the skin surface down through the dermis and up the other side of the incision to trace a flask-shaped profile (see Fig. 57.3). The wound is apposed and slightly everted. Stitches should not be tied too tightly. Nylon or polypropylene sutures are tied with three knots in alternating directions to produce a square knot. Care is exercised at sites where keloids may form (e.g. the upper back, chest or jawline), where scars may be obvious (e.g. the face of a young woman) and

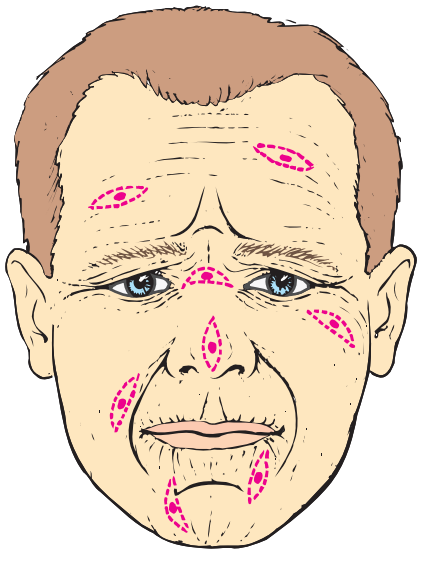


Fig. 57.2 Facial crease lines, with some examples of excision ellipses.

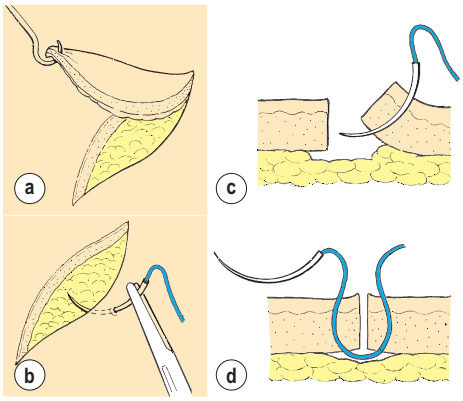


Fig. 57.3 Ellipse removal and suture insertion. (a) The ellipse is removed, one end being secured with a skin hook. (b) The suture needle is inserted vertically through the skin surface. (c) The suture needle pierces the full thickness of the epidermis and dermis. (d) The tied suture is 'flask'-shaped and slightly everts the skin surface.

Further reading – online sources

More information on basic dermatological surgery can be found at the Medscape website (access via http://emedicine.medscape.com).

Further reading – textbooks

Colver, G., 2008. Outcomes of Skin Surgery: A Concise Visual Aid. CRC Press, Boca Raton.

Lawrence, C.M., Panting, G., Raine, M., 2002. An Introduction to Dermatological Surgery. Elsevier Health Sciences, Oxford.

Robinson, J.K., Hanke, C.W., Siegel, D.M., et al., 2014. Surgery of the Skin: Procedural Dermatology. Elsevier Health Sciences, Oxford.

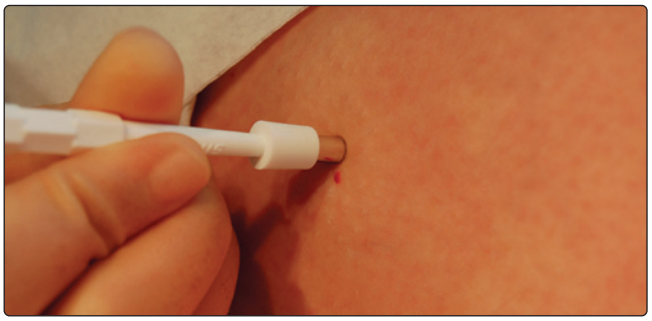


Fig. 57.4 Punch biopsy. After anaesthetizing, the skin is stretched at right angles to the tension lines, the punch blade is placed on the skin over the area to be biopsied and rotated under gentle pressure by rolling it between the thumb and the forefinger until it penetrates down to subcutaneous fat. The full-thickness cylinder of skin floats up and can be snipped off at the base. The defect is repaired with a single suture, cauterized or left to heal by secondary intention.

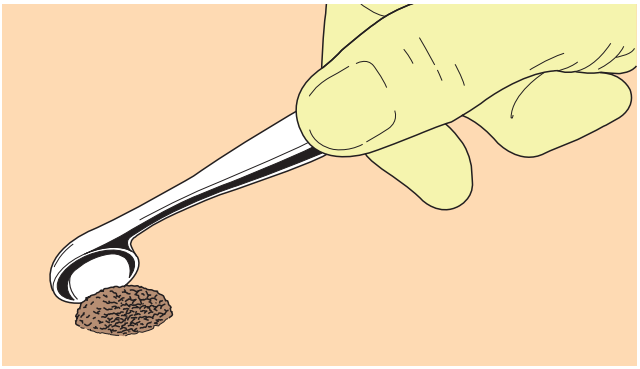


Fig. 57.5 Curettage. The lesion is removed using the curette spoon in a gentle scooping fashion. Most of the curettes now employed are disposable (use only once) ring curettes.

when healing may be poor (e.g. the lower leg). In cosmetically sensitive sites, running subcuticular stitches are preferable.

Incisional, punch and shave biopsies

An *incisional biopsy* is done for diagnostic purposes. The technique is similar to an excision except that less tissue is taken. A *punch biopsy* is a sharp circular blade, which is twisted and gently pushed into the skin to create a vertical cylindrical defect (normally 4 mm in diameter) and is used for removing small lesions or for diagnostic biopsies (Fig. 57.4).

Shave biopsy is employed for protuberant benign lesions, usually intradermal naevi or seborrhoeic warts. The lesion is shaved off parallel to, but slightly above, the skin surface. Haemostasis is achieved with cautery or hyfrecation. Not all the lesion is removed, and shaving is not used if malignancy is a possibility. Skin tags can be removed by simply snipping them off with scissors and cauterizing any bleeding points.

Curettage

Curettage is performed for seborrhoeic warts, pyogenic granulomas or single viral warts (e.g. on the face), but not for naevi or possibly malignant lesions. Basal cell carcinomas can be treated by repeated cycles of curettage and cautery but careful case selection is required. After being anaesthetized, the lesion is removed by a gentle scooping motion with the curette spoon or ring (Fig. 57.5), and then the base is cauterized. Curettings should be sent for histological analysis in 10% formalin.

Other surgical techniques

Cautery

Cautery secures haemostasis and destroys tissue. The conventional cautery machine has an electrically heated wire and is self-sterilizing. The *Birtcher hyfrecator*, a unipolar diathermy, gives better controlled electrocautery. It is used to treat spider naevi and telangiectasia, and to give haemostasis, but should not routinely be employed in patients with cardiac pacemakers. Aluminium chloride 20% in an alcohol base (Driclor; Anhydrol Forte) or silver nitrate sticks provide chemical cautery.

Cryotherapy

Cryotherapy using liquid nitrogen is effective for viral warts, molluscum contagiosum, seborrhoeic warts, actinic keratoses, *in situ* squamous cell carcinoma and, in some instances, biopsy-proven basal cell carcinoma. The liquid nitrogen (at −196°C) is delivered by spray gun (e.g. Cry-Ac) or cotton wool bud and injures cells by ice formation. After immersion in a flask containing liquid nitrogen, a cotton wool bud on a stick is applied to the lesion for about 10 s until a thin frozen halo appears at the base. The spray gun is used from a distance of about 10 mm for a similar length of freeze (Fig. 57.6). Longer freeze times are given for suitable malignant lesions. Blisters may develop within 24 h. They are punctured and a dry dressing applied. Side-effects include hypopigmentation of pigmented skin and ulceration of lower leg lesions (not recommended in this site), particularly in the elderly. Treatment is repeated after 4 weeks if necessary.

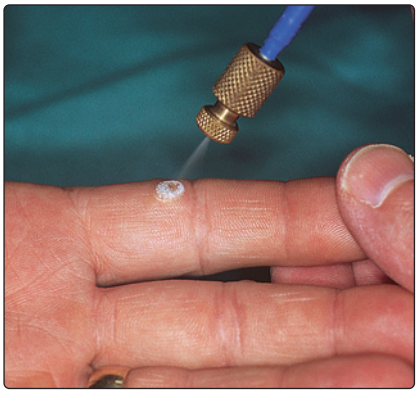


Fig. 57.6 Liquid nitrogen treatment using a cryotherapy apparatus.

Basic dermatological surgery

- **Skin surgery** is best performed in an operating theatre with aseptic technique, adequate lighting and trained nurses.
- **Local anaesthetic:** 1% lidocaine with 1/200 000 adrenaline (epinephrine) is an adequate local anaesthetic for most sites.
- **Nylon or polypropylene sutures** should be used. Smallest diameter sutures are used on the face.
- **Histopathology** is performed on all biopsy material, which needs to be labelled carefully.
- **Excisions** are done as an ellipse, parallel to the crease marks, and are about three times as long as they are wide, with 30° angles at the ends.
- **Shave biopsy** is a technique suitable for the removal of benign naevi.
- **Punch biopsy** is a useful technique for removing small lesions or for full-thickness diagnostic biopsy.
- **Curettage** is a good treatment for seborrhoeic warts, single viral warts and pyogenic granulomas.
- **Cautery**, e.g. hyfrecation, secures haemostasis and destroys tissue.
- **Cryotherapy** is used for viral and seborrhoeic warts, premalignant conditions and some tumours.

58 Advanced dermatological surgery

Some dermatologists specialize in the field of skin surgery. All registrars and residents in dermatology are trained in these techniques. An outline of the subject is given here, including the use of flaps, grafts and Mohs surgery, along with mention of lasers and photodynamic therapy, and of some basic cosmetic procedures.

Simple plastic repairs

Simple plastic repairs are carried out by the following:

- *Dog-ear excision*: dog-ears are redundant tissue at the end of an excision line. In sites of high elasticity or where tissue conservation is critical, circular excision of the lesion with appropriate margins is preferable to a predetermined ellipse excision. The redundant skin is lifted like a tent using a skin hook then excised each side ('dog ears'), and the extended wound is sutured (Fig. 58.1).
- *M-plasty*: the M-plasty is an excision that reduces the length of an ellipse where space is limited, e.g. on the face. The 'M' end of the ellipse is formed by imagining one tip of the ellipse is folded in.

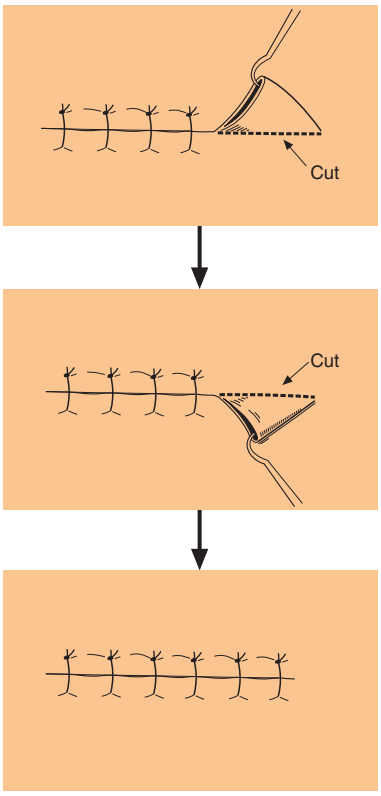


Fig. 58.1 Dog-ear repair.

Skin flaps

Side-to-side ('direct') closure of a surgical defect is often possible by undermining the edges of the wound using scissors to free the tissue but, when this is not possible, a skin graft or flap is considered. The simplest types of flap are advancement and rotation:

- *Advancement flap*: here, the skin flap is advanced in one direction over the defect. The flap of skin is created by making excision lines away from the defect to be covered, undermining to free the skin, advancing it into the defect and then suturing it in place (Fig. 58.2).
- *Rotation flap*: a defect may be covered by rotating in skin from one side. One side of the excision wound is extended as an arc that is up to three times the length of the primary defect, depending on the elasticity of the skin at that body site (the scalp and dorsal hand are the least elastic). The pedicle is undermined, rotated in to the defect and sutured in place (Fig. 58.3).

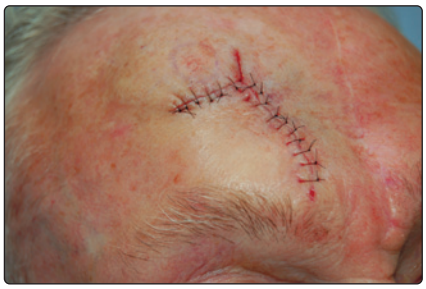


Fig. 58.2 Advancement flap of the O to L type.

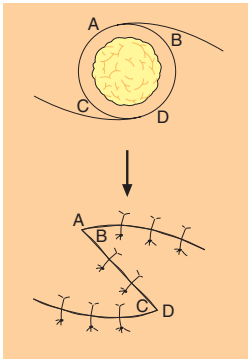


Fig. 58.3 Rotation flap.

Skin grafts

When a defect cannot be closed directly or by a flap, healing by secondary intention is often considered. This can produce excellent results on concave aspects of the nose, orbit, ear and temple, but less satisfactory appearances on convex surfaces of the nose, cheeks and chin. If it is essential to cover a defect and other techniques cannot be employed, a skin graft may be used. Skin grafts can give relatively poor cosmetic results if undertaken without careful planning and cause the added complication of creating two wounds. A graft is either full or split thickness:

- *Full thickness*: full-thickness skin is excised completely from the donor site, e.g. behind the ear or upper inner arm, which is then sutured.
- *Split thickness*: in a spilt-thickness graft, the donor site skin is cut through the dermis leaving re-epithelialization to occur from the epidermal cells of the hair follicles left behind. This method is usually used by plastic surgeons for covering large defects.

Mohs micrographic surgery

Mohs surgery describes an approach that maximizes tissue conservation by minimally excising skin cancers. Prior to skin closure, the narrowly excised tumour is examined microscopically. If the cancer is incompletely excised, the surgeon uses a mapping process to make further excisions until the margins are clear. It is indicated mostly for basal cell carcinomas that:

- are of the morphoeic type (clinical assessment of margins is unreliable)
- have recurred (scarring at site of previous excision can hide tumour cells)
- have developed in embryonic folds, e.g. nasolabial site
- require tissue conservation as a priority (e.g. on the nose, around the eyes).

The bulk of the tumour is removed by curettage and then a saucer-like piece of skin is excised. This specimen is marked and flattened, and frozen sections are taken and read immediately by microscope, giving a 'map' that shows the extent of the tumour and the areas from which further excision is needed (Fig. 58.4). The defect is repaired, sometimes in collaboration with plastic surgeons. The cure rate is 99% for basal cell carcinoma.

Table 58.1 **The application of commonly used lasers**

Source type	Source	Wavelength peaks (nm)	Vascular lesions (red)	Pigmented lesions and tattoos	Hair removal	Wrinkles, facial scars, actinic damage	Benign lesion removal
Continuous wave	CO_2	10600					Yes
Quasi-continuous wave	Potassium-titanyl-phosphate (KTP)	532	Yes	Yes (lentigines)			
	Copper vapour/bromide	510/578	Yes				
	Argon-pumped tunable dye (APTD)	577/585	Yes				
	Krypton	568	Yes				
Pulsed: long pulses or quality-switched (short pulses)	Pulsed dye laser (PDL)	585–595	Treatment of choice	Yellow, orange, red			
	Ruby	694			Yes		
	QS ruby	694		Black, blue, green, dark brown			Yes
	Alexandrite	755			Yes		
	QS Alexandrite	755		Black, blue, green, dark brown			Yes
	Diode	810			Yes		
	QS neodymium (Nd):yttrium-aluminium-garnet (YAG)	532	Yes	Purple, brown, red yellow, orange			Yes
		1064	Yes	Blue-black, dark brown	Yes		
	Erbium:YAG	2940			Yes	Yes	
	CO_2 (pulsed)	10600				Yes	Yes
	Intense pulsed light	Non-laser	Yes (PWS)	Yes (lentigines)	Yes		
Fractional (evolving field)	Erbium and others (non-ablative)	1410–1550				Yes	
	CO_2 and erbium:YAG (ablative)	2940–10600				Yes	

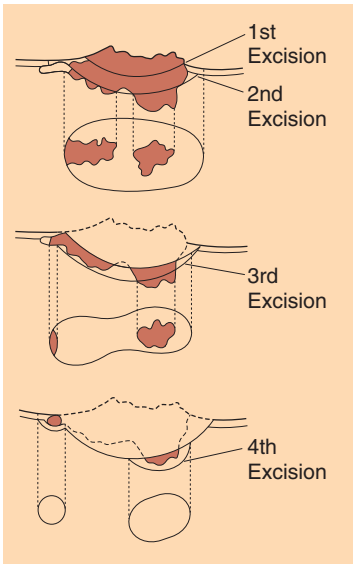


Fig. 58.4 Mohs micrographic surgery. Microscopic examination of the removed saucer of skin shows where tumour is still present and indicates the sites at which further excision is required.

Anticoagulants and antiplatelet agents

Surgical complications of bleeding can be significant (Box 58.1). Warfarin is still widely used but there is increasing use of new oral anticoagulants (NOACs e.g rivaroxaban, dagibatran) which target a non-vitamin K pathway. Although NOACs have many advantages, they also have some important differences from warfarin. NOAC status cannot be assessed by measurement of the INR and reversal of effect during bleeding is difficult, therefore surgical risk should be carefully assessed pre-operatively.

Box 58.1 **Surgical complications of bleeding**

- Perioperative or postoperative haemorrhage
- Haematoma (pain, infection)
- Wound dehiscence
- Flap or graft necrosis

Lasers and intense pulsed light (IPL)

The technology of *lasers* (*l*ight *a*mplification by *s*timulated *e*mission of *r*adiation) has advanced rapidly, and lasers can be used to treat vascular and pigmented lesions, tumours and tattoos and for hair removal. The variation in absorption of different wavelengths of light means that a range of different lasers is needed (Table 58.1). Laser therapy is carried out in specialized centres. Treatment is usually painful and several visits are often required. IPL treatment can be used for some conditions such as hair removal, and treatment is similar to laser but is a cheaper alternative. Fractional laser therapy refers to treatment of small zones within the target area patterned like the holes in a watering can rose.

Photodynamic therapy

Photodynamic therapy (PDT), in which the porphyrin precursor 5-amino-laevulinic acid is applied to a lesion that is then irradiated with visible or laser light, is very effective for extensive *in situ* squamous cell carcinoma, actinic keratoses and superficial basal cell carcinoma.

Advanced dermatological surgery

- **Dog-ear excision** removes redundant tissue at the ends of an excision to give a better quality scar.
- **Skin flaps** are used to repair a defect by the mobilization and advancement or rotation of skin.
- **Skin grafts** are used to close a defect, but secondary intention healing may give a better cosmetic result.
- **Mohs surgery** describes the microscopically controlled serial excision of difficult-to-treat skin cancers, giving a high cure rate.
- **Lasers** are used to treat vascular or pigmented skin lesions, tattoos, some skin cancers and for hair removal.
- **Photodynamic therapy** is a very effective method of treating widespread *in situ* squamous cell carcinomas.
- **Cosmetic procedures** are increasingly seen as part of dermatological practice in many countries.

Increasingly, widespread use of new anticoagulant agents has made the preparation of patients for advanced surgery more complicated. Unlike the inhibition of vitamin K activation mediated by warfarin, new anticoagulants block Factor Xa (rivaroxaban, apixaban, apixaban) or thrombin (dabigatran) independent of the vitamin K pathway and with more predictable pharmacokinetics. These drugs act quickly and there is no need to use low-molecular-weight heparin at the outset of anticoagulation. Although superior to warfarin in some settings (e.g. stroke and atrial fibrillation), they are inferior in others (e.g. prosthetic heart valves). Unlike warfarin, the international normalized ratio and partial thromboplastin time are not a reliable means to establish the anticoagulation status of the individual and although specialized tests exist, they are not routinely available. In situations of excessive bleeding, reversal of anticoagulant effects is unsatisfactory and includes oral charcoal (incomplete effect) and dialysis (for dabigatran only). Therefore, the main effect is achieved through stopping the treatment. As they are renally excreted, creatinine clearance is an important guide of the half-life. A period of 1–2 days should be adequate time to normalize anticoagulation status in healthy individuals, whereas significantly impaired renal function may require drug cessation for 6 days. In most routine skin surgery, studies have confirmed that warfarin therapy can be continued because the risk of bleeding complications is low and outweighed by the risk of thromboembolic events. Although the clinical trials have shown a similar risk of excessive bleeding, suggesting that like warfarin, these newer anticoagulants can safely be continued through skin surgery, there are few data to confirm this. Antiplatelet agents are increasingly commonly prescribed (e.g. aspirin, clopidogrel). Combination with anticoagulants is a significant risk for bleeding.

Most guidelines suggest that anticoagulants and antiplatelet treatments should be continued for minor skin surgical procedures, but careful assessment should be made.

Antiplatelet agents and skin surgery

Antiplatelet therapy is also widespread and in some situations combined with anticoagulant therapy. Aspirin (cyclooxygenase inhibitor of the arachidonic acid pathway) is the best known of these treatments. Newer agents (clopidogrel, prasugrel and ticagrelor) target the P2Y12 platelet receptor on the cell surface. During Mohs surgery, it has been shown that clopidogrel increases bleeding complications by six times more than aspirin and even more so if combined with aspirin. Clopidogrel antiplatelet effects require 1 week of drug cessation to return platelet activity to normal. Clopidogrel and warfarin combinations also significantly increase the risk of bleeding above warfarin alone. However, most guidelines suggest that these agents are continued during routine skin surgery. Prasugrel and ticagrelor are newer agents and thought to show greater platelet inhibition than clopidogrel, and have the advantage of a shorter half-life requiring only 2 days withdrawal for normal platelet function. Although it remains to be seen, it would seem reasonable to predict that bleeding complications will also be more likely with these agents. Generally, antiplatelet medications should be continued for low-risk procedures, but if taken for primary prevention only, treatment discontinuation prior to surgery can be considered.

Further reading – online sources

More information on Mohs surgery can be found at the American College of Mohs Surgery website (access via www.mohscollege.org).

More information on laser surgery can be found at the Medscape website (access via http://emedicine.medscape.com).

Further reading – textbooks

Goldman, M.P., Fitzpatrick, R.E., Ross, E.V., et al., 2013. Lasers and Energy Devices for the Skin. CRC Press, Boca Raton.

Nouri, K., 2012. Mohs Micrographic Surgery. Springer Science & Business Media, London.

59 Cosmetics and cosmetic procedures

A cosmetic is any substance applied to the body for cleansing, beautifying, promoting attractiveness or altering the appearance. The fields of cosmetology and dermatology have now converged so that patients often present having had a reaction to a cosmetic or asking for advice about cosmetic usage. Cosmetic procedures, i.e. minor surgical techniques designed to enhance the physical appearance of the skin, are now part of a dermatologist's role in many countries (though not in the UK) and are outlined here.

The range of cosmetics and their usage

Cosmetics in some form are used by almost everyone (Table 59.1). The market for cosmetic sales is vast and far exceeds that of dermatological products. Cosmetics are normally used to augment the body's appearance, to clean it, to impart a pleasing smell, to mask an unpleasant one or as a fashion accessory. Some cosmetics are marketed as 'cosmeceuticals' with the claim that they have an 'active' ingredient, e.g. one that can 'reverse ageing'.

Constituents of cosmetics

The exact contents of a cosmetic depend on its proposed function. Many cosmetics contain perfumes, preservatives and, quite often, a sunblock agent (Table 59.2). Cosmetics are often emulsions (e.g. oil-in-water or water-in-oil). Full content labelling is required in the European Union (EU). This allows patients who are allergic to cosmetic ingredients to avoid products that would be problematic. Certain preparations deserve special mention, as follows.

Paraphenylenediamine (PPD) hair dye

Hair dyes, principally PPD, are widely used. Adverse reactions occur in 5%, usually as a scalp or facial eczema. 'Henna' tattoos often contain 15–30% PPD and can induce allergy to PPD.

Table 59.1 **The range of cosmetics**

Site	Product
Skin	Moisturizer, cleanser, soap, make-up remover, powder, rouge, foundation, toner, perfume, aftershave, bath additive, sunscreen
Hair	Shampoo, conditioner, bleach, colourant, permanent waving, straightening, lacquer, gel, hair-removing agents
Eyelids	Mascara, eyeshadow, eyeliner, pencil
Nails	Nail varnish, false nails
Lips	Lipstick, lipgloss, sunscreen

Table 59.2 **Some ingredients of cosmetics**

Ingredient	Action	Examples
Antioxidant	Prevent degradation	Butylhydroxyanisole, gallates, tocopherol
Colorant, dye	Colour	Cochineal, azo compounds, iron dioxides, paraphenylenediamine, titanium dioxide, metal salts, dihydroxyacetone in fake tan
Perfume	Smell or for masking smell	*Myroxylon pereirae*, limonene, geraniol, linalool
Preservative	Antimicrobial	Parabens, formaldehyde, iodopropynyl butyl carbamate, methylisothiazolinone/chloro-methyl isothiazolinone, quaternium 15, bromo-nitropropane-diol, imidazolidinyl urea
Polyol	Humectant (retains water), emollient	Glycerol, propylene glycol, sorbitol
Oil, fat, wax	Emollient, lustre	Vaseline, almond oil, lanolin
Sun filter	Absorb or reflect UV	Titanium dioxide, oxybenzone, avobenzone
Tensioactive agent	Emulsifier, surfactant, detergent	Soaps, stearic and oleic acids
Water	Hydration	Purified water

Nail preparations

Nail varnish is composed of a tosylamide–formaldehyde resin and colourants. Artificial nails are made of methacrylate acid esters and stuck on with acrylic glues.

Sunscreens

A sunscreen absorbs or reflects ultraviolet (UV) radiation. Absorbent agents are shown in Table 59.2. Titanium dioxide and zinc oxide are reflectant pigments. The sun protection factor (SPF) indicates the ratio of the reaction time to erythema when exposed to UV radiation for treated, compared with untreated skin. Thus, using a factor 10 cream means that it should take 10 times longer for erythema to develop when in the sun. Some sunscreen creams are waterproof. Most need to be applied several times a day. Preparations available on prescription in the UK for patients with photodermatoses include: Anthelios, Sunsense Ultra and Uvistat.

Camouflage cosmetics

These pigmented camouflage creams can be mixed to match the colour of the patient's skin and are useful for individuals who have vitiligo, disfiguring birthmarks or scars. Prescribable examples include: Covermark, Dermacolor, Keromask and Veil.

Skin-lightening creams

These may contain mercury or hydroquinone, both of which can cause contact allergy or, paradoxically, pigmentation.

Hypoallergenic formulations

These cosmetics are made of highly purified ingredients, selected with the knowledge of their allergenic and irritant potential. However, they still contain compounds that are potential irritants and allergens.

Reactions to cosmetics

Side-effects are comparatively rare when the vast usage of cosmetics is considered but, nonetheless, ≥12% adults have had a reaction to a cosmetic. Some responses, e.g. stinging with aftershave due to the alcohol base, are expected and do not constitute a reaction. Some patients undoubtedly have 'sensitive' skin and react to a number of products. The preparations most likely to cause a problem are eye and facial cosmetics, antiperspirants and deodorants, hair colourants and soaps. The types of reaction are as follows:

- *Irritant contact dermatitis* is particularly seen in atopics and those with a 'sensitive' skin. Soaps, which are drying and alkaline (the normal pH of facial skin is about 5.5), and deodorants cause mostly irritant dermatitis (Fig. 59.1). Lanolins, detergents and preservatives may also be irritant.
- *Allergic contact dermatitis* usually develops at the place of application (usually the face), but not always, e.g. when tosylamide–formaldehyde resin (Fig. 59.2) in nail varnish manifests as

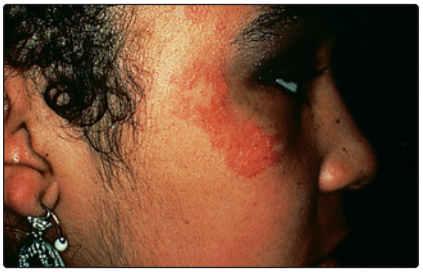


Fig. 59.1 Irritant contact dermatitis to a component of a hair-removing cream.

Side-effects are comparatively rare when the vast usage of cosmetics is considered but, nonetheless, ≥12% adults have had a reaction to a cosmetic. Some responses, e.g. stinging with aftershave due to the alcohol base, are expected and do not constitute a reaction. Some patients undoubtedly have 'sensitive' skin and react to a number of products. The preparations most likely to cause a problem are eye and facial cosmetics, antiperspirants and deodorants, hair colourants and soaps (Table e59.1). The types of reaction are as follows:

Table e59.1 **Frequent adverse reactions to cosmetics**

Cosmetic	Reaction
Soap, detergent	Mostly irritant
Deodorant, antiperspirant	Irritant, sometimes allergic
Moisturizer	Irritant and allergic
Eye shadow	Mostly irritant
Mascara	Mostly irritant
Permanent wave agent	Irritant and allergic
Hair dye (mostly PPD)	Allergic
Shampoo	Mostly irritant

- *Allergic contact dermatitis* usually develops at the place of application (usually the face), but not always, e.g. when tosylamide–formaldehyde resin (Fig. 59.2) in nail varnish manifests as dermatitis around the eyelids or neck. Common allergens include: fragrances, preservatives, dyes (e.g. PPD), lanolins, and metallic salts in some eye cosmetics (Fig. e59.1).

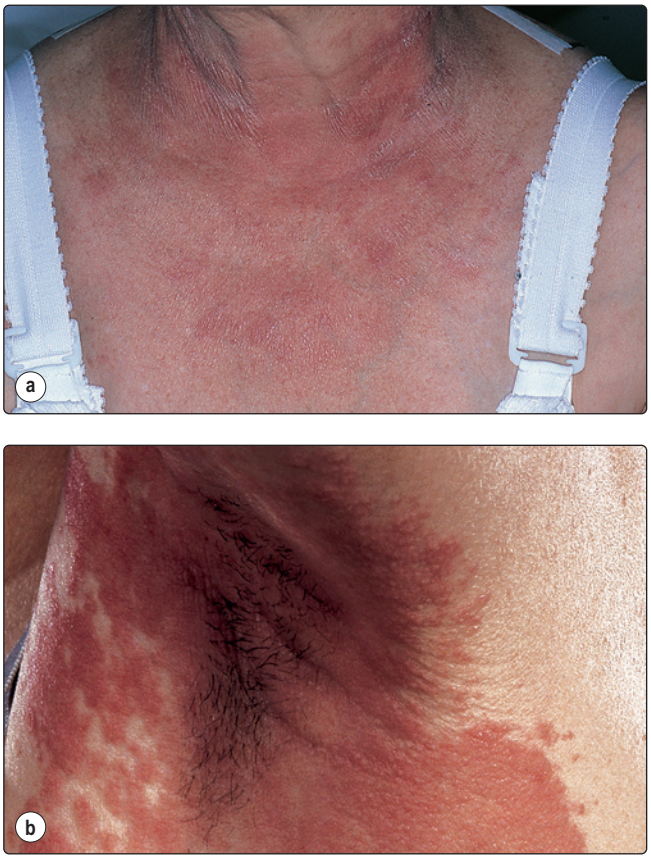


Fig. e59.1 Allergic contact dermatitis. (a) Allergic contact dermatitis on the neck due to fragrances. *(From Champion RH, Burton JL, Ebling FJG 1982 Textbook of Dermatology, 5th edition. Wiley-Blackwell, with permission.)* (b) Allergic contact dermatitis at the axilla due to a component of a roll-on deodorant.

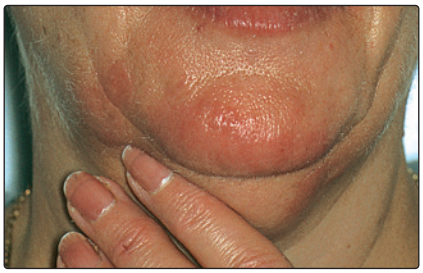


Fig. 59.2 Contact sensitivity to tosylamide–formaldehyde resin in nail varnish, causing a facial dermatitis. *(From Champion RH, Burton JL, Ebling FJG 1982 Textbook of Dermatology, 5th edition, Wiley-Blackwell, with permission.)*

dermatitis around the eyelids or neck. Common allergens include: fragrances, preservatives, dyes (e.g. PPD), lanolins, and metallic salts in some eye cosmetics.

- *Contact urticaria* (p. 80) presents as a wheal and flare response within minutes of application and may occur with perfumes, shampoos and hair dyes.
- *Tattoo reactions* can be acute irritation (erythema, swelling), infectious (e.g. hepatitis, HIV) or an allergic contact dermatitis. More chronic reactions may be lichenoid, granulomatous or pseudo-lymphomatous. Reactions to henna tattoos are usually an allergy to PPD used in the henna mixture.
- *Other adverse reactions* include nail dystrophies caused by nail cosmetic or artificial nail use, hair breakage and weathering due to improper use of permanent waving, hair straighteners or dyes, pigmentation and acne.

Management of cosmetic reactions

A patient intolerant of a cosmetic should stop the use of all cosmetics. If necessary, a topical steroid is prescribed until the reaction subsides. All products used must be examined for ingredients, and patch testing (p. 36) performed if appropriate. Alternative cosmetics can be introduced, but kept to a minimum.

Cosmetic procedures

Cosmetic procedures include the use of lasers for telangiectasia or areas of pigmentation (p. 117), botulinum toxins for wrinkles, dermabrasion, chemical peels, resurfacing and the insertion of fillers.

- *Botulinum toxins*: injection of botulinum toxins into facial muscle paralyses the action of the muscle, thus reducing the prominence of frown lines (Fig. 59.3). It is also used for axillary and sometimes palmar hyperhidrosis.
- *Dermabrasion*: the technique of dermabrasion is used for the removal of pitted or depressed scars on the face. It involves abrasive planing in a sedated and prepared patient of the epidermis and superficial dermis using a high-speed rotary brush. Regeneration of the epidermis occurs rapidly due to abundant pilosebaceous structures.
- *Laser resurfacing*: an erbium:YAG laser is used to remove the epidermis with minimal dermal damage, allowing regeneration of epidermis and the elimination of scars or photodamage. Other types of laser are used for hair removal.
- *Chemical peels*: chemical peel is an alternative to dermabrasion to improve the appearance of photodamaged or wrinkled facial skin. Alpha-hydroxy acids or weak trichloroacetic acid solutions are used.
- *Fillers*: soft tissue defects, e.g. depressed scars or wrinkles, often on the face, may be corrected by the injection of biocompatible materials such as bovine collagen or hyaluronic acid derivatives (Fig. 59.4).
- *Body sculpturing*: removal of subcutaneous body fat by liposuction to produce a slimmer body shape has been widely used. However, newer approaches for lipotransfer and lipolysis by 'subcision' (the manoeuvring of an inserted hypodermic needle under a defect to make subcuticular cuts), radiofrequency ablation and pharmacotherapy are available.
- *Hair transplant*: punch biopsies are taken from areas of normal hair density on the scalp (often the posterior hairline). The hair follicles are dissected out one by one and inserted individually into areas of alopecia.

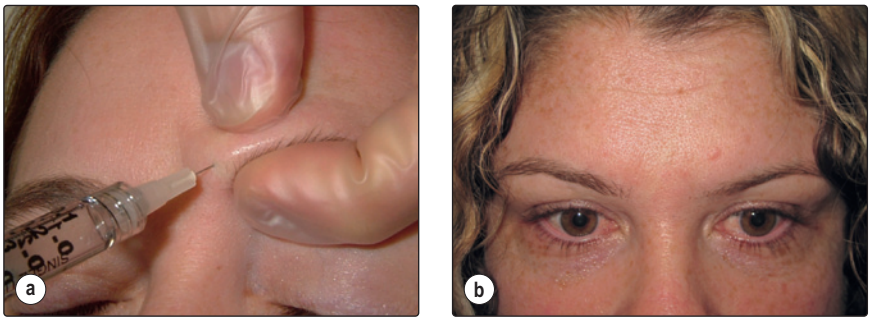


Fig. 59.3 Botox injection for glabellar frown lines. (a) The Botox is injected into the body of the corrugator supercilii muscle. (b) The patient attempting to frown. The muscle is paralysed. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

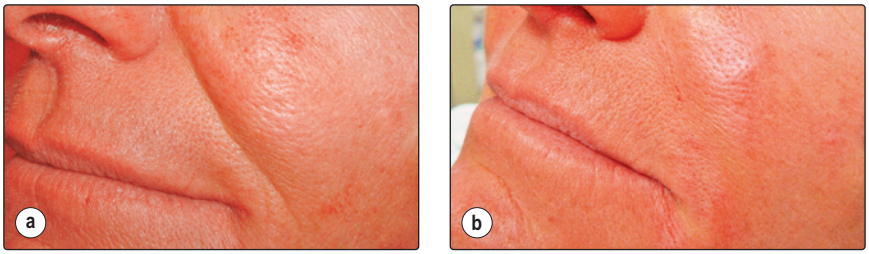


Fig. 59.4 Hyaluronic acid filler injection for facial creases. (a) The nasal fold prior to the injection. (b) The appearance after the placement of the filler. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Cosmetics

- *A cosmetic is a* substance applied to the body for cleansing, to promote attractiveness or to alter the appearance. Now used by both sexes.
- *A cosmetic cream* typically contains emollients, emulsifiers, colourants, perfumes and preservatives to prevent oxidation and the growth of microorganisms. Sun filters may also be included to prolong shelf-life and for their 'anti-photoageing' effect.
- *Reactions to cosmetics* may take the form of irritant contact dermatitis (e.g. to soaps, shampoos or deodorants) or allergic contact dermatitis (often to fragrances, preservatives or PPD), contact urticaria or pigmentary change.
- *Botox injection* is now widely used for the management of facial frown lines and for the treatment of axillary hyperhidrosis.
- *Chemical peels, lasers or dermabrasion* are used for photodamage, superficial scarring or ageing of facial skin.
- *Injection of dermal fillers* such as hyaluronic acid is used for depressed scars or facial creases.

Further reading – online sources

More information on this topic can be found at the MedicineNet website (access via http://www.medicinenet.com/).

More information on non-surgical cosmetic procedures can be obtained from the website of the British Association of Aesthetic Plastic Surgeons (access via http://baaps.org.uk).

Further reading – textbooks

The textbook edited by R. Baran and H. Maibach is useful for more advanced knowledge.

Baran, R., Maibach, H.I. (Eds.), 2010. Textbook of Cosmetic Dermatology, fourth ed. Taylor & Francis, New York.

60 Paediatric dermatology

Some conditions are almost exclusive to childhood (e.g. napkin dermatitis and juvenile plantar dermatosis), and others are more common in children (e.g. atopic eczema or viral exanthems). The common childhood dermatoses not mentioned elsewhere are detailed here along with some rare but important disorders.

Childhood eczemas and related disorders

Forms of eczema found in childhood include:

- napkin (diaper) dermatitis
- infantile seborrhoeic dermatitis
- candidiasis
- juvenile plantar dermatosis
- napkin psoriasis (p. 29)
- atopic eczema (p. 38)
- pityriasis alba (p. 44).

Napkin (diaper) dermatitis

Napkin dermatitis is the commonest type of napkin eruption. It is usually seen in infants who are only a few weeks old, and is rare after the age of 12 months. It is an irritant dermatitis due to the macerating effect of prolonged contact of the skin with faeces and urine. A glazed erythema is seen in the napkin area, sparing the skin folds. Erosions or ulceration may follow (Fig. 60.1), and hypopigmentation is a complication in pigmented skin. Secondary bacterial or *Candida albicans* infection is frequent, and the latter may account for the development of erythematous papules or pustules.

The *differential diagnosis* is from infantile seborrhoeic eczema and candidiasis, both of which tend to affect the flexures. The treatment of napkin dermatitis is aimed at keeping the area dry. The use of disposable super-absorbent nappies helps, as may more frequent changes. A bland white soft paraffin is used, with aqueous cream as a soap substitute, and a silicone-based cream (e.g. Drapolene) may have a protective action. Topical 1% hydrocortisone, with an antifungal (e.g. Daktacort or Canesten-HC), is also effective.

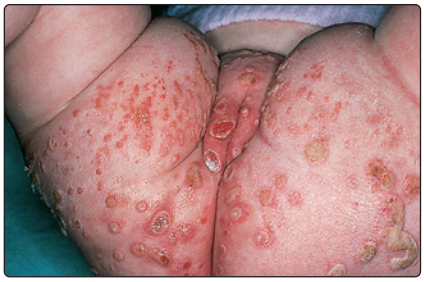


Fig. 60.1 Napkin dermatitis. A severe erosive variant is seen here.

Infantile seborrhoeic eczema

Infantile seborrhoeic eczema starts in the first few weeks of life and tends to affect the body folds, including the axillae, groin and neck, but it also may involve the face and scalp. Flexural lesions present as moist, shiny, well-demarcated scaly erythema (Fig. 60.2), but a yellowish crust is often found on the scalp. The condition can usually be differentiated from *napkin dermatitis* (which spares the flexures), *candidiasis* (which is usually pustular) and *atopic eczema* (which is more pruritic, although differentiation can be difficult in some cases). Infantile seborrhoeic eczema is treated with emollients and 1% hydrocortisone ointment, or with a hydrocortisone–antifungal combination. Scalp lesions respond to 2% ketoconazole shampoo. Olive oil will help to soften the scalp scales of cradle cap.

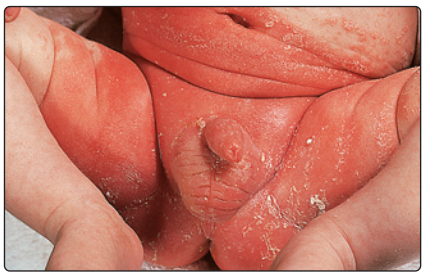


Fig. 60.2 Infantile seborrhoeic eczema. The condition involves the flexures.

Candidiasis

Infection with *C. albicans* is relatively common in the neonatal period. The organism can also secondarily complicate infantile seborrhoeic eczema or napkin dermatitis. Erythema, scaling and pustules are seen, often involving the flexures, and there may be satellite lesions. Treatment is with a topical anti-candidal agent, e.g. 2% ketoconazole cream, and 2% miconazole gel orally.

Juvenile plantar dermatosis

Juvenile plantar dermatosis, first recognized in 1968, presents with red, dry, fissured and glazed skin, principally over the forefeet but sometimes involving the whole sole (Fig. 60.3). It usually starts in the primary school years and resolves spontaneously in the early- to mid-teens. The condition is thought to be linked to the wearing of socks and shoes made from synthetic materials, although it may be a manifestation of atopy in some children. It is usual to advise cotton socks and less occlusive footwear, preferably made of leather. Topical steroids are ineffective but emollients help.

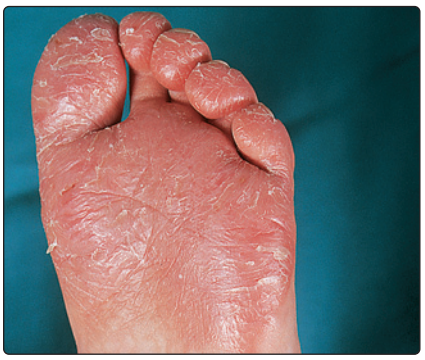


Fig. 60.3 Juvenile plantar dermatosis. The forefoot is mainly affected.

Other childhood dermatoses

Some uncommon but characteristic eruptions are found in childhood. These include:

- urticaria pigmentosa
- Langerhans cell histiocytosis
- Kawasaki disease and other viral infections (p. 55)
- ichthyosis (p. 94)
- epidermolysis bullosa (p. 95).

Urticaria pigmentosa

Urticaria pigmentosa is characterized by multiple reddish-brown macules or papules on the trunk and limbs of an infant. The lesions may become red, swollen and itchy after a bath or when rubbed, and blistering may occur. Histologically, there are accumulations of mast cells in the dermis. The disorder normally resolves spontaneously before adolescence. There is a form with a later onset, usually beginning in adolescence or adult life, which rarely resolves and may involve internal organs – something that is uncommon in the childhood variety.

Pityriasis alba is a common dermataris usually seen in childhood, in which small roundish, faintly scaly and slightly hypopigmemted patches are seen, often on the face or upper arms. It is more common in summer and appears to be a mild form of eczema (Fig. e60.1).

Napkin dermatitis is the commonest type of napkin eruption. It is usually seen in infants who are only a few weeks old, and is rare after the age of 12 months. It is an irritant dermatitis due to the macerating effect of prolonged contact of the skin with faeces and urine. A glazed erythema is seen in the napkin area, sparing the skin folds. Erosions or ulceration may follow (Fig. 60.1), and hypopigmentation is a complication in pigmented skin. Secondary bacterial or *Candida albicans* infection is frequent, and the latter may account for the development of erythematous papules or pustules (Fig. e60.2).

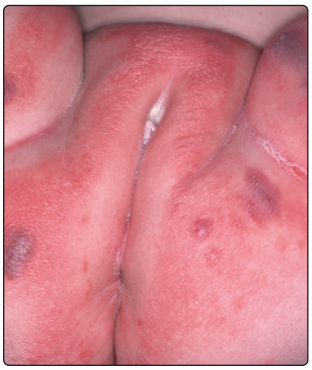


Fig. e60.2 Napkin dermatitis. This variant shows gluteal granulomas. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

Napkin psoriasis

Psoriasis is uncommon in infancy and red scaly napkin eruptions are more likely to be psoriasiform manifestations of napkin dermatitis or infantile seborrhoeic dermatitis. Genuine napkin psoriasis may occur in infancy perhaps through koebnerization in a genetically predisposed individual (Fig. e60.3). A definitive diagnosis of psoriasis is, however, difficult and few infants who present with this go on to develop psoriasis in adult life.

Urticaria pigmentosa is characterized by multiple reddish-brown macules or papules on the trunk and limbs of an infant (Fig. e60.4). The lesions may become red, swollen and itchy after a bath or when rubbed, and blistering may occur. Histologically, there are accumulations of mast cells in the dermis. The disorder normally resolves spontaneously before adolescence. There is a form with a later onset, usually beginning in adolescence or adult life, which rarely resolves and may involve internal organs – something that is uncommon in the childhood variety.

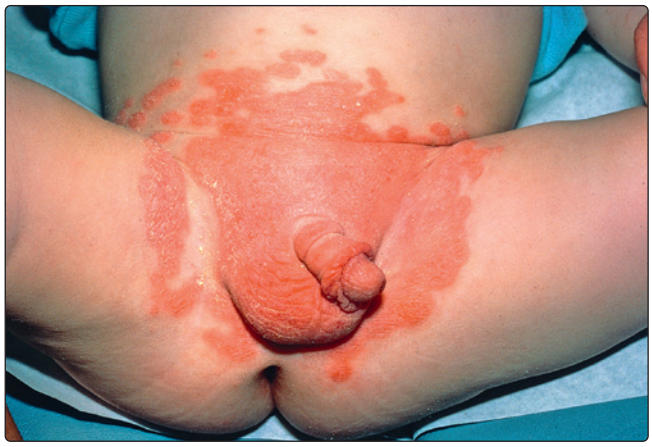


Fig. e60.3 Napkin psoriasis. The features are those of a confluent dry scaly erythema with sharply defined rather scalloped edges. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

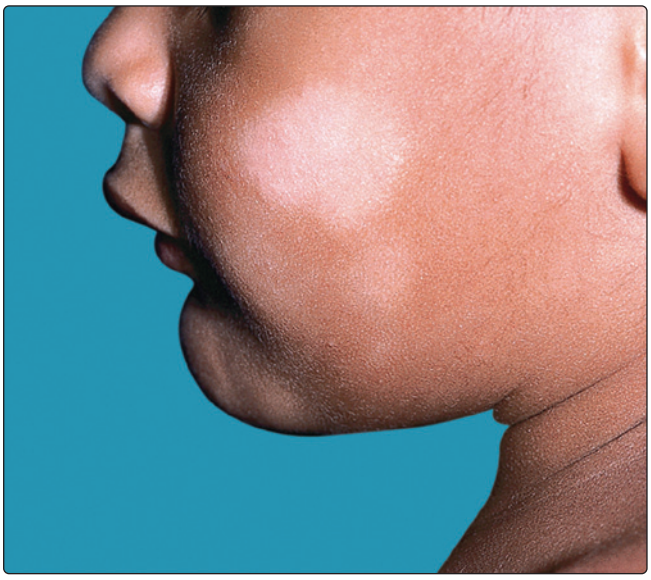


Fig. e60.1 Pityriasis alba. A hypopigmented slightly scaly patch on the left cheek. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

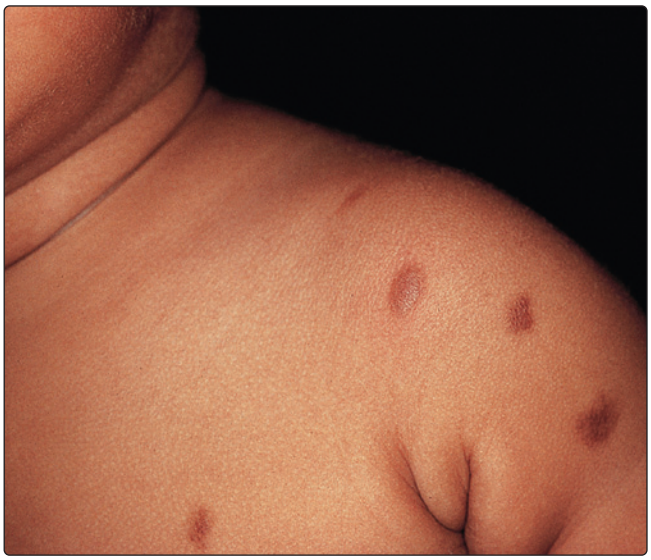


Fig. e60.4 Mastocytosis nodules of juvenile urticarial pigmentosa. Scattered nodules on the chest and shoulder are evident. They show some hyperpigmentation and slight surrounding erythema. Darier's sign of urtication on rubbing a lesion is virtually pathognomonic. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Langerhans cell histiocytosis (histiocytosis X)

Langerhans cell histiocytosis is a rare and serious condition that normally involves internal organs. The skin signs are common, variable and include a seborrhoeic-like dermatitis, papules or pustules on the trunk and ulceration, particularly of the flexures. The skin, abdominal organs, lungs and bones are infiltrated by clonal Langerhans cells, which may behave in a malignant fashion, although the condition is believed to be reactive and not a true malignancy. Skin biopsy is usually diagnostic. The prognosis is poorer when the onset is before 2 years of age.

Vascular naevi

Vascular naevi are common and are present at birth or develop soon after. Superficial lesions are due to capillary networks in the upper or mid dermis, but larger angiomas show multiple vascular channels in the lower dermis and subcutis.

Clinical presentation

There are four main clinical pictures, which are described below.

Salmon patch

This is the commonest vascular naevus, seen in 20–60% of neonates. Patches at the upper eyelid fade quickly, but the 'stork mark' at the posterior neck persists in 20–30% of cases. Parents should be reassured; no investigation or treatment is required.

Port-wine stain naevus

Present at birth, the port-wine stain (or *naevus flammeus*) is an irregular red or purple macule that often affects one side of the face (Fig. 60.4), although other sites can be involved. Lesions vary from millimetres to centimetres in diameter. In middle age, it can darken and become lumpy. A port-wine stain involving the ophthalmic division of the trigeminal nerve may have an associated intracranial vascular malformation (the *Sturge–Weber syndrome*). Port-wine stains near the eye can be associated with glaucoma.

Infantile haemangioma

Infantile haemangiomas appear shortly after birth. Most occur on the head or neck and grow to reach a maximum in the first 12 months (Fig. 60.5). They remain static for the next 6–12 months and then involute. Most cases will have regressed by the age of 5–7 years, leaving an area of atrophy. Infantile haemangiomas are classified as superficial (e.g. strawberry naevus), deep or mixed, and can be localized or segmental. The deep type, e.g. cavernous haemangioma, is composed of larger and deeper vascular channels and presents as a nodular bluish swelling. The overlying skin may be normal or show a superficial vascular component (i.e. be mixed). Regression is not as complete as in the superficial type. Ulceration with bleeding and secondary infection can develop. Large haemangiomas may trap platelets and cause thrombocytopenia (the *Kasabach–Merritt syndrome*). In segmental haemangiomas, abnormalities in the underlying organs should be suspected.

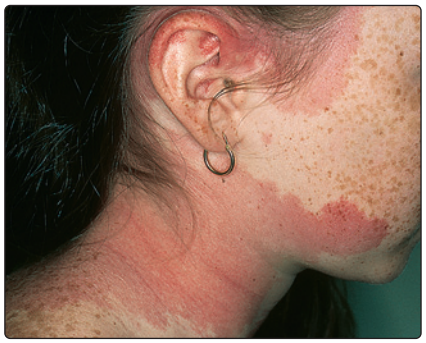


Fig. 60.4 Port-wine stain naevus. These are often present at birth. Neurological and ophthalmological assessments may be needed. Early treatment with a flashlamp-pulsed dye laser is often recommended.

Fig. 60.5 Strawberry naevus in an infant. These haemangiomas develop during the first few weeks of life but often involute by the age of 5–7 years. Treatment is needed if they compromise vital structures such as the eye.

Arteriovenous malformation (AVM)

Aberrant vascular channels may occur in the skin, subcutis or deeper structures. Arteriovenous fistulae can be found, e.g. in a limb, and hypertrophy of the involved part sometimes is seen.

Management

Port-wine stains may be covered with camouflage cosmetics (p. 118), but treatment is now available with the flashlamp-pulsed dye laser (p. 117), which obliterates the abnormal dermal vessels and improves the appearance. A child with a facial port-wine stain needs neurological and ophthalmic assessment. Infantile haemangiomas should be allowed to involute unless they compromise vital structures such as the eye or airway. In this case, a short course of oral propranolol (starting dose 1mg/kg per day) is now the treatment of choice (prednisolone was previously used). The Kasabach–Merritt syndrome is treated with systemic steroids, cytotoxic agents (e.g. vincristine), embolization or surgery, depending on response. Haemangiomas at the lower back may have associated tethering of the spinal cord; a neurological assessment and imaging are indicated. An AVM requires the opinion of a vascular surgeon.

Paediatric dermatology

Disorder	Age at onset	Clinical features
Napkin dermatitis	First few weeks to 12 months	Glazed erythema that spares body folds Erosions may occur
Infantile seborrhoeic eczema	First few weeks	Moist scaly erythema Flexures and scalp affected
Candidiasis	Infancy	Erythema, with scaling and pustules Flexures affected Secondary infection found
Juvenile plantar dermatosis	School-age to mid-teens	Glazed red fissured skin on the forefeet and soles
Urticaria pigmentosa	Mostly at 3–9 months	Reddish-brown macules or papules on trunk, which urticate when rubbed
Langerhans cell histiocytosis	All ages (different types)	Seborrhoeic-like dermatitis, papules/pustules, ulceration
Vascular naevi	At birth, in first few weeks	Salmon patch on neck, port-wine naevus (e.g. on face), strawberry naevus

Langerhans cell histiocytosis is a rare and serious condition that normally involves internal organs. The skin signs are common, variable and include a seborrhoeic-like dermatitis, papules or pustules on the trunk and ulceration, particularly of the flexures (Fig. e60.5). The skin, abdominal organs, lungs and bones are infiltrated by clonal Langerhans cells, which may behave in a malignant fashion, although the condition is believed to be reactive and not a true malignancy. Skin biopsy is usually diagnostic. The prognosis is poorer when the onset is before 2 years of age.

Miliaria crystallina

Miliaria occurs when the flow of sweat from the eccrine sweat ducts is blocked (in adults it is known as 'prickly heat'). Miliaria crystallina is common in the neonatal period and tends to affect the upper half of the body. It occurs when the portion of the sweat duct in the stratum corneum is obstructed due to delayed patency. The eruption presents as crops of clear thin-walled superficial vesicles, 1–2 mm in diameter (Fig. e60.6). These rupture within 1 day and desquamate.

Surgery is considered for anatomically vital sites such as the periorbital region, if pharmacological therapies fail.

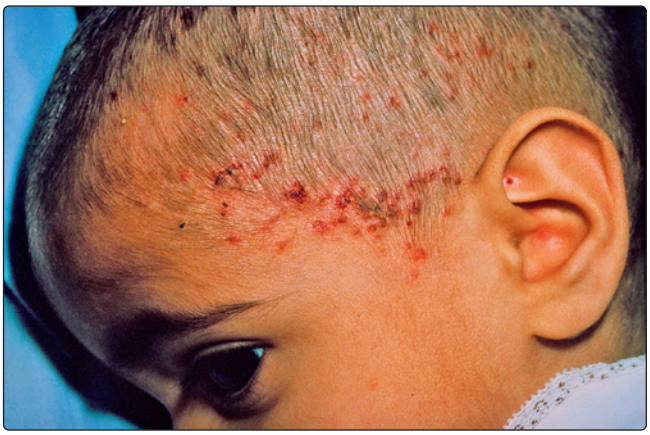


Fig. e60.5 Langerhans cell histiocytosis. The disease may present with a seborrhoeic dermatitis-like eruption on the scalp but papules and crusting are more prominent than would be anticipated in an eczema. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

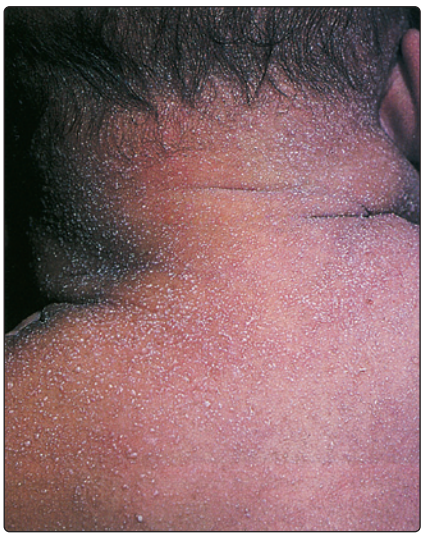


Fig. e60.6 Miliaria crystallina. Tiny superficial vesicles are seen on the back and neck of a newborn. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Further reading – online sources

For further information on paediatric dermatology readers are referred to the emedicine website (access via http://www.emedicinehealth.com/).

Further reading – textbooks

Eichenfield, L.F., Frieden, I.J., Mathes, E.F., Zaenglein, A.L. (Eds.), 2015. Neonatal and Infant Dermatology, third ed. Elsevier, London.

Irvine, A.D., Hoeger, P.H., Yan, A.C. (Eds.), 2011. Harper's Textbook of Pediatric Dermatology, third ed. Blackwell, Oxford.

61 The skin in old age

In Westernized societies, the proportion of people aged over 65 is high and continues to rise. Poor nutrition, lack of self-care and general illness contribute to skin disease in the elderly. Few people die from old skin, but many suffer from it.

Intrinsic ageing of the skin

The changes in aged, sun-protected skin are more subtle than those of photoageing (p. 113.e1) and consist of laxity, fine wrinkling and benign neoplasms. In addition, androgenetic alopecia (p. 70) and greying of the hair are age-related.

Histologically, the epidermis is thinned with the loss of the rete ridge pattern and a reduction in the numbers of melanocytes and Langerhans cells. Individual epidermal cells are smaller. The dermis is thinned due, mainly, to loss of proteoglycans. Functionally, the skin is less elastic and has a reduced tensile strength. Resistance to injury, irritants and infection is reduced, and wound healing is slower.

Some inherited disorders, e.g. pseudoxanthoma elasticum (p. 97), show features of aged skin. The misuse of potent topical steroids induces atrophy and purpura (p. 23), signs also seen in old skin.

Dermatoses in the elderly

Few skin conditions are exclusive to old age, but some are seen more frequently (Table 61.1).

Dry skin and asteatotic eczema

Dryness with itching is common in elderly skin. It may be a mild roughness and scaling, or more severe, with fissuring and inflammation (asteatotic eczema, p. 41). The changes often occur on the legs and are aggravated by low humidity, central heating and excessive washing. Emollients, sometimes with a mild or moderate potency topical steroid ointment, usually help.

Seborrhoeic dermatitis (p. 40) in the elderly (Fig. 61.1) may be flexural and resemble psoriasis, candidiasis or erythrasma. In old people, *allergic contact dermatitis* (p. 36) to allergens in topical medicaments or toiletries, e.g. lanolin, neomycin, fragrances and local anaesthetics, particularly needs to be considered.

Pruritus

Itch in old age can be severe and unrelenting. Examination will usually show asteatotic eczema, scabies, urticaria or the prebullous phase of pemphigoid (p. 82), or investigations may reveal renal or liver disease or underlying malignancy (p. 88.e1). The small group of patients in whom no cause is found have *'senile pruritus'*. Topical treatments and sedating antihistamines are often ineffective.

Psoriasis

Psoriasis has its peak onset in the teens with a second peak in the sixth decade. In the elderly patient, it is frequently flexural (p. 29), but all patterns, except guttate, are seen. Management can be difficult due to inability to apply topical therapy, attend hospital or stand for ultraviolet treatment. Methotrexate is used quite often and is mostly well tolerated.

Infections and infestations

Herpes zoster (p. 57) at some time affects 25% of people over 65. Post-herpetic neuralgia increases with age, occurring in 75% of shingles victims over 70. Early treatment with antivirals (e.g. aciclovir) together with amitriptyline or gabapentin makes neuralgia less likely.

Infection with *Candida albicans* (p. 63) is common in the flexures of obese elderly women. *Onychomycosis* (p. 61) is a frequent incidental finding in old people, especially men. Treatment is not always needed unless the nail produces pain.

Scabies epidemics are a problem in old people's homes and are difficult to control (p. 67). Any itchy old person should be examined carefully, as burrows are easily missed. Elderly patients who are debilitated, paralysed, immunosuppressed or who cannot scratch may develop crusted 'Norwegian' scabies (Fig. 61.2), which is highly contagious due to the thousands of mites present.

Table 61.1 **Skin disorders common in the elderly**

The eczemas (see Chs 18, 19, 20)	Asteatotic/dry skin Seborrhoeic Contact Venous
Other eruptions (see Chs 14, 37, 45)	Psoriasis Drug eruption Erythema ab igne
Infections (see Chs 28, 30, 31, 33)	Herpes zoster Candidiasis Onychomycosis Scabies
Ulceration (see Chs 38, 61)	Leg ulcer Pressure ulcer
Autoimmune (see Ch 41)	Pemphigoid
Benign tumours (see Ch 49)	Seborrhoeic wart Cherry angioma Skin tag Chondrodermatitis nodularis
Photodamage (see Ch 56)	Photoageing Actinic elastosis
Premalignant (see Ch 51)	Actinic keratosis *In situ* squamous cell carcinoma
Cancers (see Chs 52, 53, 54, 55)	Basal cell carcinoma Squamous cell carcinoma Lentigo malignant melanoma Cutaneous T cell lymphoma
Other	Senile pruritus

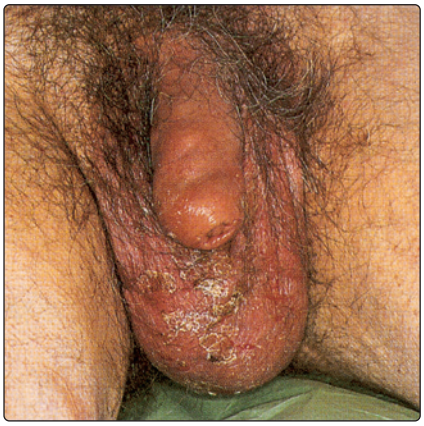


Fig. 61.1 Flexural seborrhoeic dermatitis affecting the scrotum and penis.

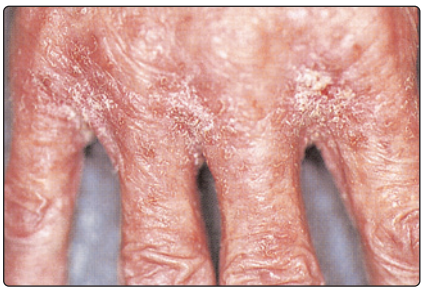


Fig. 61.2 Crusted 'Norwegian' scabies.

Further reading – online sources

More information on skin ageing can be found at the MedlinePlus website (access via http://www.nlm.nih.gov/medlineplus/skinaging.html).

Further reading – textbooks

Not many textbooks focus on the skin in old age:

Minaker, K.L., 2011. Common clinical sequelae of aging. In: Goldman, L., Schafer, A.I. (Eds.), Goldman's Cecil Medicine, twenty-fourth ed. Elsevier Saunders, Philadelphia. (Ch. 24).

Individual diseases are best reviewed in standard texts:

Bolognia, J.L., Jorizzo, J.L., Schaffer, J.V. (Eds.), 2012. Dermatology, third ed. Elsevier Saunders, Philadelphia.

Burns, T., Breathnach, S., Cox, N., Griffiths, C. (Eds.), 2010. Textbook of Dermatology, eighth ed. Blackwell, Oxford.

Photodamage and skin tumours

Most benign and malignant skin tumours are more common in the elderly (Table 61.1). Many are related to sun exposure. Specific disorders of photodamage include:

- *Actinic (solar) keratoses*: (see Ch. 51 and Fig. 61.3). A *cutaneous horn* may occasionally develop in an actinic keratosis (Fig. 61.4). It is best treated by excision.
- *Actinic (solar) elastosis*: in solar elastosis, the sun-exposed skin is yellowed, thickened and wrinkled. On the neck, furrowed rhomboidal patterns are sometimes seen (Fig. 61.5), particularly in those with outside occupations such as farmers. 'Senile' comedones or thickened yellowish plaques may develop. Photodamage is worse in smokers.
- Damaged dermal collagen with inflammation in the dermis and cartilage is a feature of *chondrodermatitis nodularis* (p. 99, Fig. 61.6). Treatment is by excision, although some early lesions can be halted by topical glucocorticoid treatment.

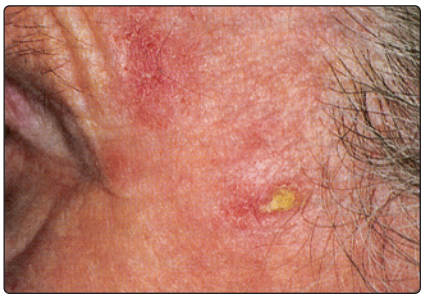


Fig. 61.3 Actinic keratoses.

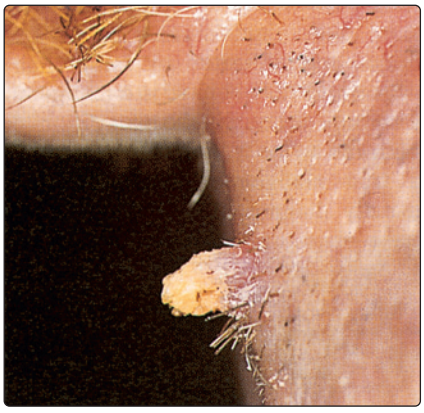


Fig. 61.4 A cutaneous horn.

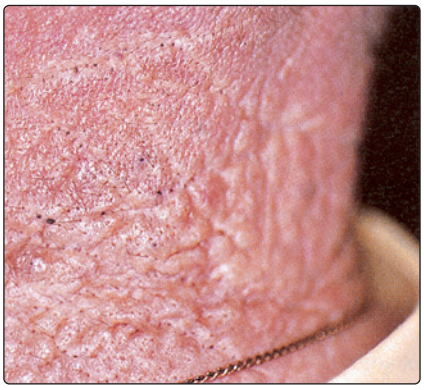


Fig. 61.5 Actinic elastosis. The characteristic rhomboid pattern is seen on the neck, associated with senile comedones. A history of chronic sun exposure, often occupational, is invariably obtained.

- *Actinic cheilitis*: excessive exposure to sun, often occupational, can induce inflammation and scaling of the lower lip. Treatment options are the same as for actinic keratoses. Diagnostic histology is recommended in thickened, tender or new lesions because squamous cell carcinoma can be missed.

Ulceration

- *Leg ulcers*: venous ulcers often start in middle age but, because of their chronicity, are a problem in the elderly. Ischaemic ulcers become more common with advancing years (p. 77).
- *Pressure ulcers*: a pressure ulcer starts as an area of erythema and progresses to widespread necrosis of tissue with ulceration. Deep ulcers develop over the sacrum (Fig. 61.7), heels, ischia and greater trochanters. Secondary infection with *Pseudomonas aeruginosa* is common.

Pressure ulcers mainly occur in the elderly who are recumbent and immobile, e.g. due to a fractured femur, arthritis, unconsciousness or paraplegia. Malnutrition, reduced cutaneous sensation and arterial disease predispose to tissue breakdown.

Prevention is possible if at-risk patients are identified. Regular repositioning, the use of an antipressure mattress and attention to diet and to the patient's general condition help in prevention and treatment. A necrotic eschar separates by itself in 2–4 weeks. The resulting ulcer can be covered by a semipermeable dressing, e.g. Opsite. Proteolytic enzymes (Varidase) may be used to debride heel lesions. Pain relief is vital. Surgical excision and flap repair are possible provided the patient's general condition is satisfactory.

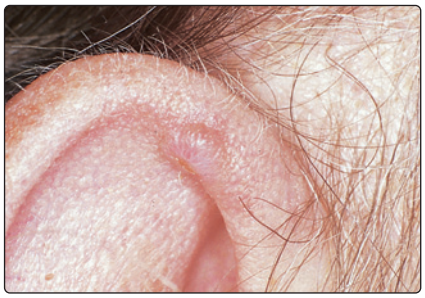


Fig. 61.6 Chondrodermatitis nodularis.

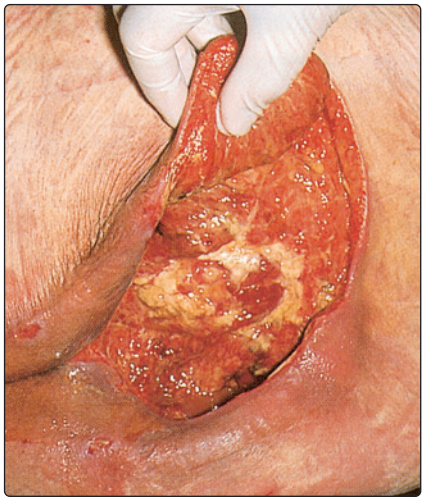


Fig. 61.7 Pressure ulcer over the sacrum.

The skin in old age

- **Asteatotic eczema** (also known as eczema craquelé) is a dry, scaly, fissured eruption that commonly affects the elderly. Treatment is with emollients and mild topical steroids.
- **Pruritus** in old people nearly always has a cause. Scabies, urticaria or prebullous pemphigoid are easily missed. Investigation for underlying systemic disease may be indicated.
- **Herpes zoster** is common in old age. Aciclovir or famciclovir may make neuralgia less likely.
- **Actinic keratoses** are roughened hyperkeratotic areas in sun-exposed sites. They are often treated by cryosurgery or the application of fluorouracil cream or diclofenac gel.
- **Actinic elastosis** is a yellowed, thickened, wrinkled change in sun-exposed skin, e.g. on the neck, often seen in men who have had outdoor occupations.
- **Pressure ulcers** result from reduced sensation, immobility, malnutrition and ischaemia. It is vital to identify at-risk patients and institute means to prevent these ulcers from developing.

62 The skin in pregnancy

All skin conditions may arise in pregnancy and pre-existing conditions may worsen or improve. The most important consideration is for the health of the unborn baby, which often makes treatment more difficult. Only a few systemic treatments are recognized to be safe in pregnancy.

The skin during pregnancy

The changes in the skin during the pregnant state can be categorized as physiological changes due to endocrine effects, the effects of stretching and the effects of the alteration in immune function of pregnancy on skin disease. Some dermatoses are pregnancy-specific and some are exacerbated by pregnancy.

Normal physiological effects arise in most pregnancies, and are consequences of the endocrine changes. These effects include pigmentary alterations, hair and nail changes, vascular proliferation and sebaceous gland activity.

Pigmentary changes such as hyperpigmentation are common in pregnancy e.g. melasma (p. 79) and linea nigra (abdominal midline pigmentation), and generally recede post-partum. Melanocytic naevi may also darken and sometimes enlarge.

Stretch marks (striae gravidarum), are pinkish, linear changes arising in later pregnancy on skin which has stretched (e.g. abdomen, breasts). Post-partum these gradually fade, but are usually permanent (striae alba). Little evidence exists that topical treatments are preventative.

Hair and nails can become brittle. Hair shedding 1–5 months post-partum represents telogen effluvium (p. 70) and usually resolves spontaneously.

Vascular changes such as telangiectasia and pyogenic granulomas are also more prevalent in pregnancy. Venous dilation in the lower half of the body (e.g. leg varicosities, haemorrhoids) due to partial obstruction of venous return and venous thromboses are also more common.

Acne may arise de novo or worsen in pregnancy due to increased sebum production. Retinoids should be avoided, but topical or oral erythromycin is usually considered safe.

Dermatoses in pregnancy

Few skin conditions are exclusive to pregnancy, but some are seen more frequently. Pruritus is common in pregnancy (approx. 17%), and the differential diagnosis includes: idiopathic pruritus (pruritus gravidarum, prurigo of pregnancy), eczema, urticaria, scabies, pediculosis, drug eruptions and obstetric cholestasis (Table 62.1). Non-itchy conditions are also prevalent, but usually more easily distinguished, including erythema nodosum, solitary tumours, changing moles and physiological changes (see above).

Infections

Pregnancy is considered a partially immunocompromised state, which is necessary to permit the support of the HLA tissue antigen mismatch with the fetus. Consequently, infections in pregnancy are common, and more severe compared with non-pregnant women. Of these, viral and fungal infections are the commonest problems identified. Viral exanthems, including varicella and measles, do not usually need specific management for the skin, other than topical emollients but discussion of systemic therapy with a medical obstetrician is recommended. Herpes simplex virus infections (genital and extra-genital) are at increased risk of dissemination and hepatitis, hence requiring prompt treatment with antivirals (usually oral acyclovir, which is not known to be harmful in pregnancy). Infections in the third trimester are at increased risk of neonatal herpes and prophylactic treatment should be considered in those women with recurrent herpes. Viral warts can grow fast and be challenging to treat, and although podophyllin should not be used in pregnancy, the standard destructive modalities are acceptable: cryotherapy, electrocautery, laser therapy, surgery or trichloroacetic acid.

Fungal infections, including candida are common in pregnancy, and usually best treated with imidazole creams (e.g. clotrimazole), which are thought only to be minimally absorbed through the skin and not known to be harmful, but oral imidazoles, e.g. itraconazole are not recommended. Terbinafine cream (and orally) is not recommended either. Bacterial infections of the skin are usually treated, as normal, with antibiotics that are not known to be harmful (e.g. erythromycin and flucloxacillin). Infestations with scabies and lice are usually treated with topical permethrin cream, which is not known to be harmful and is more effective than malathion or benzyl benzoate. Oral ivermectin is contraindicated.

Table 62.1 **Conditions presenting with pruritus in pregnancy**

Condition	Frequency (%)
Eczema in pregnancy[a]	49.7
Polymorphic eruption of pregnancy	21.6
Cutaneous infections/ infestations	5.3
Pemphigoid gestationis	4.2
Intrahepatic cholestasis of pregnancy	3.0
Pityriasis rosea	2.8
Acne (involving face and trunk)	2.6
Drug reactions	2.4
Contact dermatitis	2.2
Urticaria (other than drug induced)	1.6
Psoriasis	1.2
Lichen planus	1.0
Prurigo gravidarum[a]	0.8
Lupus erythematodes	0.6
Haemorrhagic pigmented dermatosis	0.4
Pruritic folliculitis of pregnancy[a]	0.2
Leukocytoclastic vasculitis	0.2
Linear IgA dermatosis	0.2
Pemphigus vulgaris	0.2

[a]These conditions are difficult to distinguish and are sometimes grouped as atopic eruption of pregnancy (AEP).
(From Ambros-Rudolph CM, Mullegger RR, Vaughan-Jones SA et al. 2006. J Am Acad Dermatol 54:395–404.)

Pregnancy-specific dermatoses

Intrahepatic cholestasis of pregnancy (ICP) is diagnosed by demonstration of pruritus without an underlying inflammatory skin disease (scratch marks only) in the presence of elevated total serum bile acid levels. This condition poses increased risks to mother

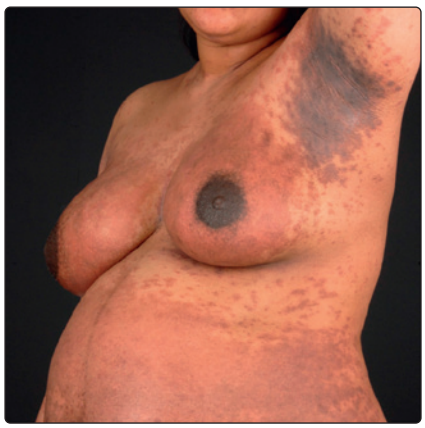


Fig. 62.1 Atopic eczema of pregnancy. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Pigmentary changes

Generalized, mild hyperpigmentation is common in pregnancy but may be accentuated in specific sites, including groins, flexures and especially in the abdomen midline (linea nigra). Melanocytic naevi may also darken and sometimes enlarge. Hyperpigmentation generally recedes postpartum, but some changes, e.g. vulvar melanosis, may persist. The symmetrical, macular hyperpigmentation on the cheeks of melasma is also common and exacerbated by sun exposure (p. 79). Hypopigmented, pinkish, linear changes are frequently noted in later pregnancy, and their location at sites of enlargement on the breasts, thighs and abdomen has led to the name 'stretch marks' also known as 'striae gravidarum'. Histologically, the dermal elastin is and collagen fibrils are disorganized and likely contribute to the weakened tensile strength. Over time, the lesions fade to eventually become pale, often shiny, atrophic linear changes (striae alba) that are permanent. Despite widespread use of emollients and oils to reduce striae during pregnancy, little evidence exists that this is effective.

Hair and nails

Nails can become brittle and show changes of leukonychia, and even Beau's lines (transverse ridges), but non-pregnancy causes should also be excluded. Thickening of the hair due to follicular enlargement and increased terminal hair growth, causing a hirsute appearance in some pregnancies, is well recognized but such changes resolve after the pregnancy. In the period 1–5 months following delivery, shedding of the scalp hair caused by increased hair cycling from anagen to telogen, known as telogen effluvium (p. 70), is very common. Although many women find this distressing, most cases typically resolve within 6–12 months.

Vascular changes

An increase in dynamic circulation results in palmar erythema and flushing, while partial obstruction of venous return can cause venous distention of the lower half of the body. Leg varicosities are common, but can also arise on the vulva, vagina and anus (haemorrhoid). Deep venous thrombosis must be considered in unilateral or painful leg swelling. Proliferation of blood vessels is associated with the development of spider naevi and angiomata, but pyogenic granulomas are also more common in pregnancy.

Sebaceous glands

During pregnancy, the sebum production is increased, which can result in seborrhoea or exacerbations and de novo cases of acne. This is typically apparent in late pregnancy but may arise earlier. Topical and oral retinoids are strongly contraindicated and severe cases can be difficult to treat. Oral erythromycin is considered a safe option.

(intrapartum haemorrhage, cholelithiasis) and fetus (meconium staining, premature delivery and intrauterine death). ICP is usually treated with ursodeoxycholic acid (UDCA), which settles the itch and improves the liver biochemistry, but the benefit to fetal outcomes is uncertain. This condition usually worsens as pregnancy progresses and resolves 48–72 h after delivery. Recurrence in future pregnancies is common.

Atopic eruption of pregnancy arises in the first and second trimester in those with a background history of atopy and is defined by a pruritic rash which can affect flexures (as classical atopic eczema) or non-flexural sites with excoriated papules and nodules (Fig. 62.1). Some papules may be follicular and show sterile pustulation. There are no specific diagnostic tests and therapy principles are based around the management of atopic eczema. Avoidance of soaps, regular emollients and use of mild corticosteroid creams are the mainstay of treatment. Antihistamines are often beneficial and are generally considered not to be harmful (e.g. cetirizine and loratadine), except for hydroxyzine (where toxicity has been shown with high doses). The use of potent topical corticosteroids should be limited to avoid systemic effects, but in severe cases, short courses of oral prednisolone may be indicated. Other treatment options include phototherapy, ciclosporin and azathioprine.

Pemphigoid gestationis (PG) previously known as herpes gestationis, arises in the second and third trimester of pregnancy and is characterized by a pruritic eruption consisting of urticated papules (Fig. 62.2) and plaques progressing to bullae (Fig. 62.3). Typically, the condition involves the umbilicus initially and spreads in a centrifugal manner. The face, mucous membranes, palms and soles are generally spared. Flaring of the disease postpartum is recognized. Skin biopsy is critical to the diagnosis and on direct immunofluorescence, shows features similar to bullous pemphigoid, i.e. linear C3 ± IgG at the dermo-epidermal junction. Pemphigoid gestationis is associated with low birthweight and premature delivery. Mild cases may be managed with topical corticosteroids and antihistamines, but most women require oral prednisolone 0.5 mg/kg per day. Although the dose should be tapered as far as possible after disease control, it is advisable to increase it at the time of delivery to prevent disease flares. Other treatment options including ciclosporin and IVIg are occasionally considered.

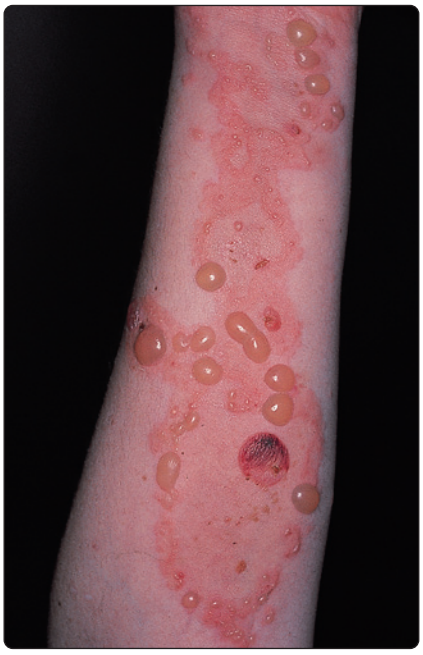


Fig. 62.2 Pemphigoid gestationis. Grouped tense bullae on an urticarial base in a woman with pemphigoid gestationis. *(From Callen JP, Jorizzo JL, Bolognia JL, Piette WW, Zone JJ 2003 Dermatological Signs of Internal Disease, 4th edition. Saunders, with permission.)*

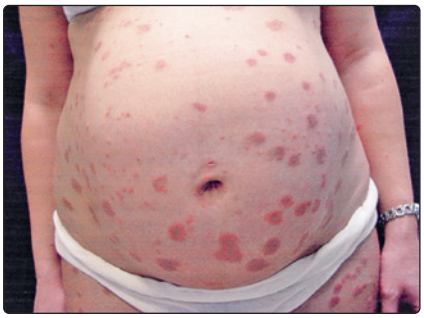


Fig. 62.3 Pemphigoid gestationis. Multiple urticarial lesions, many of which have small vesicles on the periphery. *(From Callen JP, Jorizzo JL, Bolognia JL, Piette WW, Zone JJ 2003 Dermatological Signs of Internal Disease, 4th edition. Saunders, with permission.)*

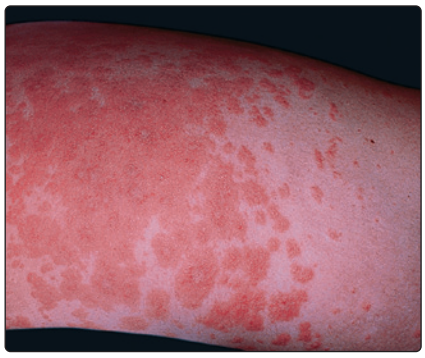


Fig. 62.4 Polymorphic eruption of pregnancy. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

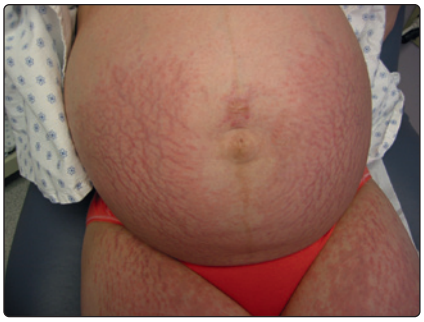


Fig. 62.5 Polymorphic eruption of pregnancy within and around prominent abdominal striae. *(From Callen JP, Jorizzo JL, Bolognia JL, Piette WW, Zone JJ 2003 Dermatological Signs of Internal Disease, 4th edition. Saunders, with permission.)*

Polymorphic eruption of pregnancy (PEP)

Pruritic urticarial papules and plaques of pregnancy (PUPPP; syn. PEP) usually begins at the end of the third trimester of pregnancy (Fig. 62.4). In contrast to PG, PEP typically is first noted on the lateral abdominal skin (often in striae gravidarum) and spares the umbilicus (Fig. 62.5). As described in the name, the clinical features are variable but are mainly intensely pruritic urticated papules and plaques. Blisters are very uncommon and if identified, consideration of PG should be made. PEP does not confer any risk to the mother or fetus and usually resolves 1–2 weeks postpartum, but often recurs in future pregnancies. Diagnosis is usually clinical but if there is doubt, is confirmed by negative direct immunofluorescence. Moderate potency topical corticosteroids are usually effective, but more potent formulations, oral corticosteroids and phototherapy have been used in severe cases.

Skin changes in pregnancy

- **Endocrine effects of pregnancy** induce physiological changes in the skin such as hyperpigmentation, hair growth and increased sebum production.
- **Pruritus** is very common in pregnancy and has a wide number of possible causes.
- **Prurigo gravidarum** is a common problem for which no specific cause is identified.
- **Atopic eczema of pregnancy** is very common and usually starts in the first trimester of pregnancy. Treatment with emollients and topical corticosteroids is similar to childhood atopic eczema.
- **Pemphigoid gestationis** is an autoimmune disorder which arises in pregnancy causing urticated plaques and blisters, typically involving the umbilicus. This can be severe and often requires oral steroid therapy.
- **Polymorphic eruption of pregnancy** usually starts after 35 weeks of pregnancy and typically involves the stretch marks, sparing the umbilicus. PEP is a benign condition that usually responds to topical therapy and antihistamines.

Pruritic urticarial papules and plaques of pregnancy (PUPPP; syn. PEP) usually begins at the end of the third trimester of pregnancy (Fig. 62.4 and Fig. e62.1). In contrast to PG, PEP typically is first noted on the lateral abdominal skin (often in striae gravidarum) and spares the umbilicus (Fig. 62.5 and Fig. e62.2). As described in the name, the clinical features are variable but are mainly intensely pruritic urticated papules and plaques. Blisters are very uncommon and if identified, consideration of PG should be made. PEP does not confer any risk to the mother or fetus and usually resolves 1–2 weeks postpartum, but often recurs in future pregnancies. Diagnosis is usually clinical but if there is doubt, is confirmed by negative direct immunofluorescence. Moderate potency topical corticosteroids are usually effective, but more potent formulations, oral corticosteroids and phototherapy have been used in severe cases.

Further reading – online sources

More information on the skin in pregnancy can be found at the Medscape website (access via http://emedicine.medscape.com).

Further reading – textbooks

Black, M.M., Ambros-Rudolph, C., Edwards, L., et al., 2008. Obstetric and gynecologic dermatology. Elsevier Health Sciences, Oxford.

Readers are also referred to the standard texts:

Bolognia, J.L., Jorizzo, J.L., Schaffer, J.V. (Eds.), 2012. Dermatology, third ed. Elsevier Saunders, Philadelphia.

Burns, T., Breathnach, S., Cox, N., Griffiths, C. (Eds.), 2010. Textbook of Dermatology, eighth ed. Blackwell, Oxford.

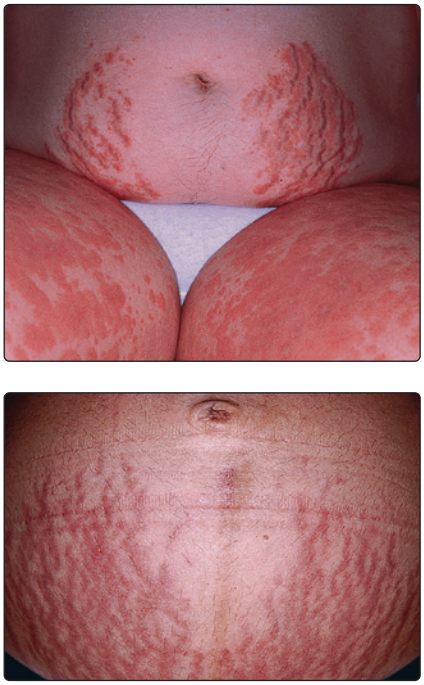


Fig. e62.1 Polymorphic eruption of pregnancy.

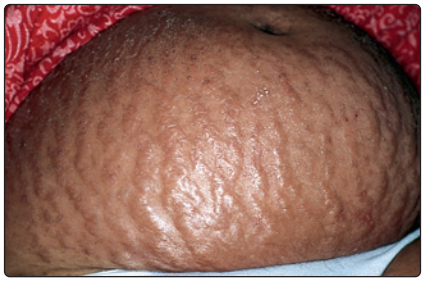


Fig. e62.2 An urticated pregnancy-associated eruption often starts in abdominal striae.

63 Genitourinary infections

In the UK and Ireland, genitourinary medicine has traditionally been a separate specialty from dermatology, but the two are combined as 'dermatovenereology' in many countries. It has become increasingly important for those treating skin disease to know more about genitourinary disorders. Genitourinary diseases range as follows (see also Table 63.1): syphilis, gonorrhoea, human immunodeficiency virus (HIV) infection (Ch. 29), chlamydial infection, pelvic inflammatory disease, vaginitis, chancroid, viral warts (p. 54), genital herpes simplex (p. 56), hepatitis B and hepatitis C, vulval/perianal dermatoses, and penile/scrotal dermatoses. The latter diseases are described in Chapter 64.

Table 63.1 **Other genitourinary infections**

Condition	Organisms	Clinical features	Therapy
Non-gonococcal urethritis	*Chlamydia trachomatis* *Ureaplasma urealyticum* *Mycoplasma genitalium*	Males: dysuria, frequency, urethral discharge or asymptomatic	Single dose of azithromycin 1 g orally or doxycycline 100 mg twice daily for 7 days
Chlamydial mucopurulent cervicitis	*Chlamydia trachomatis* (exclude *Neisseria gonorrhoeae*)	Females: asymptomatic or yellow cervical exudate	Single dose of azithromycin 1 g orally or doxycycline 100 mg twice daily for 7 days or erythromycin
Pelvic inflammatory disease	*Chlamydia trachomatis* *Neisseria gonorrhoeae* Anaerobes *Gardnerella vaginalis* *Mycoplasma genitalium*	Acute abdominal pain and tenderness, fever, raised white blood cell count	Intramuscular ceftriaxone followed by oral doxycycline *plus* metronidazole or oral ofloxacin *plus* metronidazole for 14 days
Vaginitis	*Trichomonas vaginalis* *Gardnerella vaginalis* *Bacteroides* *C. albicans*	Asymptomatic or erythema, itch and discharge: male partners get urethritis and balanitis	Oral metronidazole 2 g single dose or 400–500 mg twice daily for 5–7 days; alternatively Tinidazole 2 g orally single dose
Chancroid	*Haemophilus ducreyi*	Single or multiple tender, necrotic, erosive ulcers	Azithromycin 1 g oral single dose (or ciprofloxacin, erythromycin, or IM ceftriaxone)
Hepatitis B	Hepatitis B virus	~40% show any symptoms	Vaccinate at-risk groups; Peginterferon alfa-2a, entecavir and other antiviral agents

Syphilis (Lues)

Syphilis is a chronic infectious disease due to *Treponema pallidum*. Skin signs are seen in all three stages.

Clinical presentation

T. pallidum may rarely be acquired congenitally or from a contaminated blood transfusion, but the normal mode of transmission is through sexual intercourse.

- *Primary chancre*. About 3 weeks after sexual contact, a primary chancre, a painless ulcerated button-like papule, develops at the site of inoculation. This is usually genital (Fig. 63.1), but oral and anal chancres are seen in men who have sex with men. Regional lymphadenopathy is common. Without treatment, the chancre clears spontaneously in 3–10 weeks. Serology is not positive until 4 weeks after infection, but spirochaetes can be isolated from the chancre.
- *Secondary stage*. This phase starts 4–10 weeks after the onset of the chancre. It is characterized by a non-itchy pink or copper-coloured papular eruption on the trunk, limbs, palms and soles (p. 45; Fig. 63.2). Untreated, the eruption resolves in 1–3 months. Serology is positive.
- *Tertiary stage*. About 30% of patients with untreated syphilis will develop late lesions, usually after a latent period of years. Painless nodules, sometimes with scaling, develop in annular or arcuate patterns on the face or back. Subcutaneous granulomatous gumma – usually on the face, neck or calf – ulcerate, scar and never heal completely (Fig. 63.3). Cardiovascular syphilis and neurosyphilis may coexist.

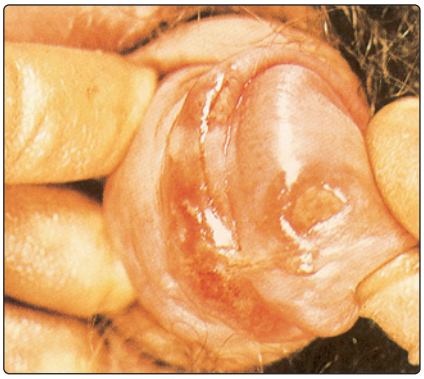


Fig. 63.1 Primary chancre of syphilis. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

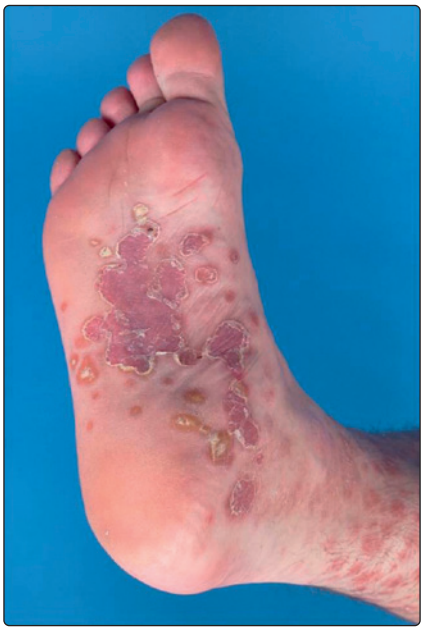


Fig. 63.2 Secondary syphilis. Coalescing pink papules with a collarette of scale, on the sole and lower leg.

Management

Primary or secondary syphilis is treated with a single dose of benzathine penicillin G 2.4 MU i.m. or doxycycline 100 mg PO twice daily for 2 weeks, or Azithromycin 1 g PO single dose. All patients should be offered screening for HIV and need contact tracing and assessment for other venereal diseases. Alternative regimens are required for pregnancy and children, and are best undertaken in conjunction with those with experience of genitourinary medicine.

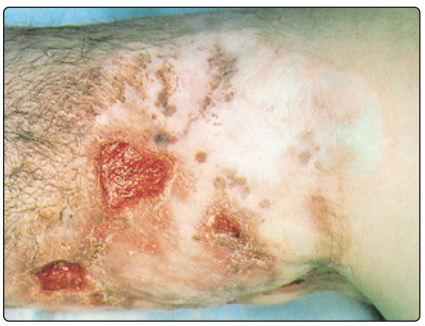


Fig. 63.3 Gumma of tertiary syphilis. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

Further reading – online sources

More information on GU medicine can be found at the British Association of Sexual Health and HIV website (access via www.bashh.org).

Further reading – textbooks

Pattman, R., Sankar, N., Elawad, B., et al., 2010. Oxford Handbook of Genitourinary Medicine, HIV, and Sexual Health. OUP, Oxford.

Genitourinary diseases are also reviewed in standard texts:

Bolognia, J.L., Jorizzo, J.L., Schaffer, J.V. (Eds.), 2012. Dermatology, third ed. Elsevier Saunders, Philadelphia.

Burns, T., Breathnach, S., Cox, N., Griffiths, C. (Eds.), 2010. Textbook of Dermatology, eighth ed. Blackwell, Oxford.

Gonorrhoea

Gonorrhoea is caused by the Gram-negative diplococcus *Neisseria gonorrhoeae*. Infection may be symptomatic or asymptomatic and may be detected with culture or nucleic acid amplification tests.

Clinical presentation

Symptomatic males usually present with dysuria, frequency of micturition and a purulent urethral discharge. Females, when symptomatic, can have an abnormal vaginal discharge, dysuria, intermenstrual bleeding, menorrhagia or abdominal pain. Pharyngeal and anorectal infection may produce symptoms or may be asymptomatic. The diagnosis relies on the microscopic identification of Gram-negative intracellular diplococci from urethral (males and females) or endocervical (females) smears, and culture for *N. gonorrhoeae*. Serological tests are unreliable. Women with untreated gonorrhoea are at risk of developing pelvic inflammatory disease and infertility. In men, complications include urethral stricture, infertility and epididymitis.

Gonococcaemia is rare but, when observed, results in fever, arthritis and pustules that are few in number and generally distributed on the hands, feet or near the large joints (Fig. 63.4). This is a type of septic vasculitis which, as with some other systemic infections (e.g. *Neisseria meningitidis*), may be purpuric.

Management

Uncomplicated acute gonorrhoea should be treated with single-dose ceftriaxone (500 mg i.m.) or azithromycin (1 g) oral as a single dose (or both together for pharyngeal infections). Combination regimes of azithromycin and single doses of oral cefixime or spectinomycin are alternatives, as determined by microbiological sensitivities. Infection acquired abroad should be presumed to be multiantibiotic resistant. Pharyngeal and rectal infection may be particularly difficult to eliminate. A repeated culture to test for a cure is made 4–7 days after treatment. Patients with gonorrhoea should be screened for coexisting sexually transmitted diseases, e.g. chlamydia. Management is most appropriate in a department of genitourinary medicine where contact tracing can be organized.

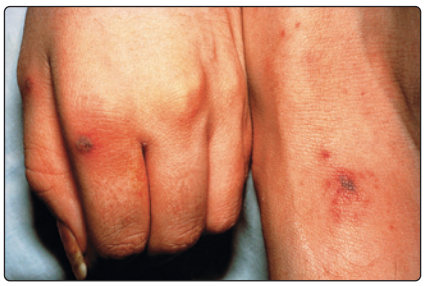


Fig. 63.4 Gonococcaemia. Scattered inflammatory pustules are evident over joints. *(From James WD, Berger TG, Elston DM 2011 Andrews' Diseases of the Skin, 11th edition. Saunders, with permission.)*

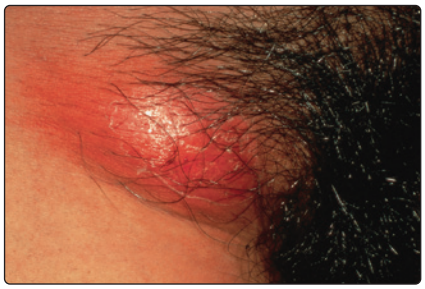


Fig. 63.5 Chancroid. Unilateral inguinal lymphadenitis is shown with overlying erythema. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Other genitourinary infections

Chlamydia and genital warts (p. 54) in the UK are currently the most common genitourinary infections, with rates respectively of about 1,000 and 600 per 100,000 population. Most cases present to a department of Genitourinary medicine.

Genital chlamydia has no cutaneous symptoms or signs. It may present in men with urethral discharge or dysuria, and in women with vaginal discharge or dysuria, but many infections, especially in females, are asymptomatic (Table 63.1). Pelvic inflammatory disease develops in 10–40 percent of infected women. Reiter's syndrome can be a complication in infected men and women (p. 44).

Other genitourinary infections are less common in western countries. When seen they have usually been acquired in tropical countries. Example include the following:

Lymphogranuloma venereum (or inguinale) is caused by certain serovars of *Chlamydia trachomatis* that primarily infect the lymphatics. It causes a localised ulcer which is followed by inguinal swellings that may progress to bubos, accompanied by malaise. After several years, lymphatic obstruction with gross genital lymphedema can result.

Chancroid, caused by *Haemophilus ducreyi*, is characterised at the site of inoculation, by an inflammatory papule, which may ulcerate and in the process, facilitate HIV infection. In some cases inguinal lymphadenopathy develops which can progress to bubo formation (Fig. 63.5). Patients with chancroid should be screened for infection with HIV.

Granuloma inguinale, also known as Donovanosis, is caused by *Klebsiella granulomatis*. It presents on the genitalia as an ulcerating nodule that ulcerates, enlarges, and typically becomes necrotic with secondary infection. Genital disfigurement and potentially malignant change, may develop.

Genitourinary infections

Syphilis

- The primary chancre appears 3 weeks after sexual contact.
- The papular non-pruritic eruption of the secondary stage is seen 4–10 weeks following the chancre.
- Tertiary syphilis may be delayed several years.
- Treatment is with benzathine penicillin, doxycycline or azithromycin.
- Patients need contact tracing and should be screened for other venereal diseases.

Gonorrhoea

- Men present with dysuria, frequency and a urethral discharge.
- Women complain of a vaginal discharge, dysuria and abdominal pain.
- Infection may be asymptomatic.
- Late sequelae include pelvic inflammatory disease and infertility.
- Treatment is with a single oral dose of ceftriaxone or azithromycin but should be guided by local trends in antimicrobial resistance.

Genital chlamydia

- Women are often asymptomatic, but may present with vaginal discharge or dysuria.
- Men may be asymptomatic or present with urethral discharge, dysuria or frequency.
- Genital chlamydia has no primary cutaneous manifestations.
- Treatment is with a single oral dose of azithromycin or a course of oral doxycycline.

Pelvic inflammatory disease

- Presents in women with lower abdominal pain and tenderness, fever and malaise.
- Caused by various infections including gonococcus, chlamydia, and anaerobic organisms.
- Long term sequelae include infertility, ectopic pregnancy and chronic pelvic pain.
- Treatment is with a combination of antibiotics, including metronidazole, doxycycline, ceftriaxone and ofloxacin.

64 Genital dermatoses

The genital and perianal skin can be involved by the same disease processes that affect skin elsewhere, although the appearances may be different. The genital skin is also subject to specific disease processes that may present diagnostic difficulties to non-experts (and sometimes to experts). Infections of genital skin are dealt with elsewhere in this book.

Female genital dermatoses

Skin diseases of the vulva have often proved confusing (even to dermatologists) because the usual characteristics of the eruption are lost or modified, making diagnosis more difficult.

Benign dermatoses

Itching (pruritus vulvae) is a common symptom in vulval disease and is often followed by secondary lichenification. Frequently seen conditions include: psoriasis (p. 28), eczemas including allergic contact dermatitis (Fig. 64.1) and seborrhoeic dermatitis (p. 62) and common infections such as herpes simplex (p. 56), viral warts (p. 54), candidiasis (p. 62) and venereal infections (p. 126). Dermatoses with a specific focus on female genital skin include:

- *Lichen sclerosus* (p. 43) can affect women of any age, involving the genito-crural folds, the inner labia majora, labia minora and clitoris. The involved skin shows an atrophic whitened epithelium sometimes with purpura and erosions (Fig. 64.2). Scarring from lichen sclerosus alters the genital architecture with loss and fusion of the labia minora and narrowing of the introitus. The treatment is with topical clobetasol propionate. The risk of developing squamous cell carcinoma is 4%.
- *Lichen planus* (p. 42) of the vulva appears as violaceous papules, plaques or erosions, sometimes with a white lacy border. It occurs as part of a generalized eruption (p. 42) or as a pigmented flexural or erosive mucosal syndrome. Treatment is with a topical steroid.
- *Pigmentary changes* include vulval melanosis (a biopsy is usually needed to exclude malignancy) and depigmentation, e.g. due to vitiligo.

Neoplasia

- *Vulval intraepithelial neoplasia* (VIN; the terms Bowen's disease and bowenoid papulosis are no longer used) is either undifferentiated (associated with oncogenic human papilloma virus types 16 and 18) or the differentiated type seen with lichen sclerosus and which has a high risk of squamous cell carcinoma (Fig. 64.3). Cervical intraepithelial neoplasia can coexist with undifferentiated VIN, and screening is required. Treatment is by excision (for small areas), topical fluorouracil or imiquimod, and laser therapy. Follow-up is needed.
- *Squamous cell carcinoma* occurs as two types. The largest group is in elderly women, where the cancer has developed in a background of chronic lichen sclerosus (or lichen planus). The smaller group is in younger women where the tumour arises in association with HPV infection. The presentation is a nodule, often ulcerated, frequently within an area of diseased skin. Specialist surgical excision is needed.
- *Other tumours*. Basal cell carcinoma and malignant melanoma can be found in the vulval area, as can extramammary Paget's disease (p. 92).

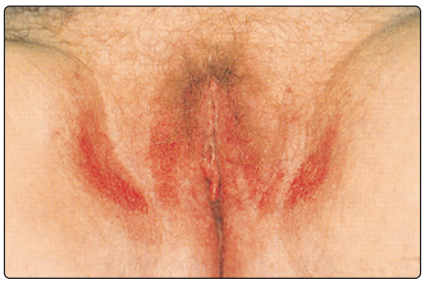


Fig. 64.1 Contact dermatitis of the vulva. This was caused by allergy to neomycin in a cream

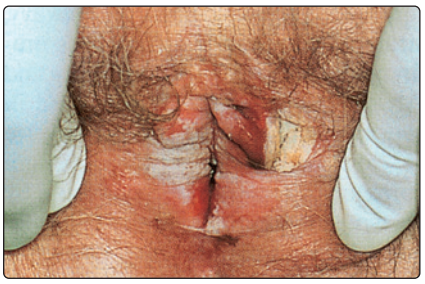


Fig. 64.3 A hyperkeratotic variant of vulval intraepithelial neoplasia (VIN).

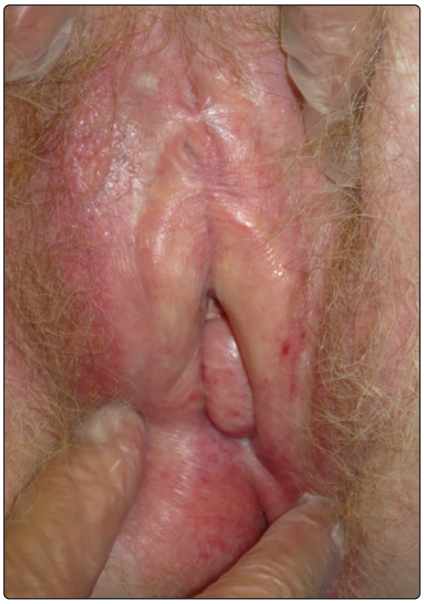


Fig. 64.2 Lichen sclerosus of the vulva showing loss of the normal architecture, atrophy and purpura. *(Courtesy of Dr Fiona Lewis, St Thomas Hospital, London.)*

Genital ulceration and trauma

- *Genital ulceration* may occur in benign aphthae and with pemphigoid or pemphigus (p. 82), or acutely with erythema multiforme. It is also seen with Behçet's syndrome, a multisystem disorder in which recurrent oral aphthous ulceration and iridocyclitis also occur.
- *Female genital mutilation* results in removal of the clitoris or narrowing of the introitus. Genital trauma can indicate abuse.

Pain syndromes

- *Vulvodynia* is defined as 'vulval pain in the absence of any infective, inflammatory, neoplastic or neurological disorder'. It is divided into a generalized spontaneous type (not requiring touch), as seen in older women, or localized provoked pain (vestibulodynia).
- *Vestibulodynia* usually presents in young women, who complain of dyspareunia and vestibular tenderness to light touch. A variety of treatments are tried including topical local anaesthetics, measures to control pain (e.g. oral gabapentin or amitriptyline) and psychological support.

Itching (pruritus vulvae) is a common symptom in vulval disease and is often followed by secondary lichenification. Frequently seen conditions include: psoriasis (p. 28), eczemas including allergic contact dermatitis (Fig. 64.1) and seborrhoeic dermatitis (p. 62) and common infections such as herpes simplex (p. 56), viral warts (p. 54), candidiasis (p. 62, Fig. e64.1) and venereal infections (p. 126). Dermatoses with a specific focus on female genital skin include:

- *Lichen sclerosus* (p. 43) can affect women of any age, involving the genito-crural folds, the inner labia majora, labia minora and clitoris. The involved skin shows an atrophic whitened epithelium sometimes with purpura and erosions (Fig. 64.2 and Fig. e64.2). Scarring from lichen sclerosus alters the genital architecture with loss and fusion of the labia minora and narrowing of the introitus. The treatment is with topical clobetasol propionate. The risk of developing squamous cell carcinoma is 4%.
- *Crohn's disease*. Anogenital involvement in Crohn's disease is seen in about a 30% of cases, either by direct extension of active intestinal disease or as metastatic disease. The presentation is varied with ulceration, abscess formation, fistulae and swelling. Biopsy shows granulomatous changes.

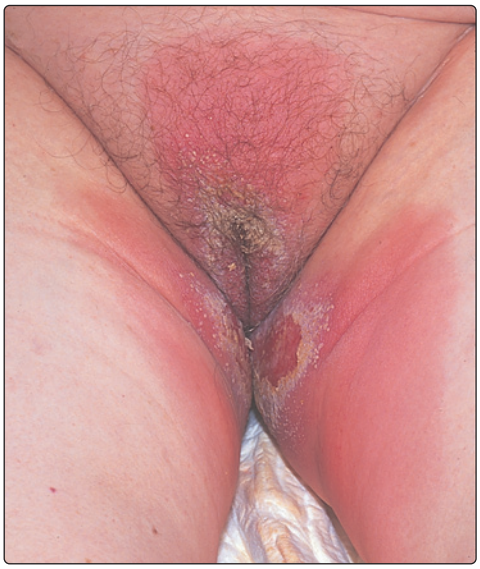


Fig. e64.1 A severe erosive form of candidal vulvitis. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

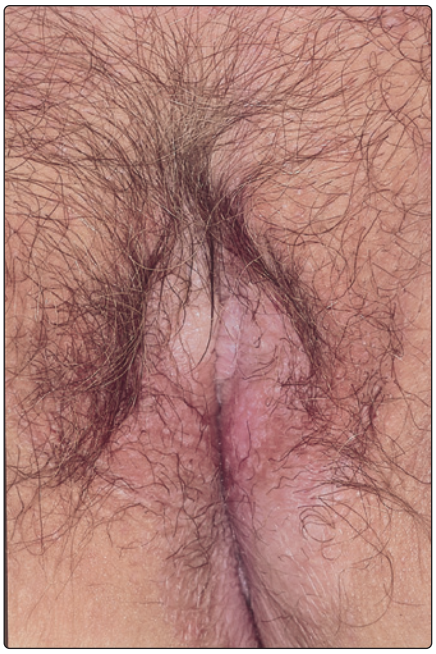


Fig. e64.2 Lichen sclerosus of the vulva showing typical white sclerotic changes. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

Male genital dermatoses

The glans penis, foreskin (prepuce) and scrotum can be involved by diseases involving the rest of the skin, such as eczema and psoriasis.

Benign dermatoses

Dermatoses with a specific focus on the male genitalia:

- *Balanitis* describes inflammation of the penile skin, e.g. by eczema (Fig. 64.4). *Circinate balanitis* is an eroded or crusted penile eruption seen in Reiter's syndrome (p. 44).
- *Lichen sclerosus* has a predilection for the penis (p. 42). White plaques are seen sometimes with haemorrhagic areas, erosion and sclerosis. The glans, especially around the urethral meatus, is often involved (Fig. 64.5). The severe end result can be balanitis xerotica obliterans (where the meatal aperture is considerably narrowed) or phimosis. Treatment is with a highly potent topical steroid (clobetasol propionate). Chronic lichen sclerosus can predispose to squamous carcinoma (in up to 10% of cases).
- *Zoon's balanitis* presents as well-demarcated glistening moist red or brown patches on the glans or inner foreskin (Fig. 64.6). It tends to affect uncircumcised middle-aged or elderly males and seems to be a reaction to irritant factors. Topical steroids can help but the condition is often refractory.

Neop lasia

- *Penile intraepithelial neoplasia (PIN)*. The terms 'erythroplasia of Queyrat', 'Bowen's disease' and 'bowenoid papulosis' are all variants of PIN (i.e. carcinoma in situ of the penis). PIN presents as patches of warty or scaly plaque on the penile shaft or foreskin, or more moist red patches on the mucosal glans. It is associated with human papilloma virus (especially HPV 16) and HIV infection. Treatment is as for VIN.
- *Squamous cell carcinoma* presents as an irregular often ulcerating nodule on the penis. Biopsy and urgent surgical referral are needed.
- *Cysts and tumours of the scrotum*. Epidermoid cysts are not uncommon in the scrotum. They are excised if troublesome. Squamous cell carcinoma of the scrotum presents as an irritating nodule, often ulcerated. It can be occupationally induced by exposure to carcinogens (e.g. soot, mineral oils).

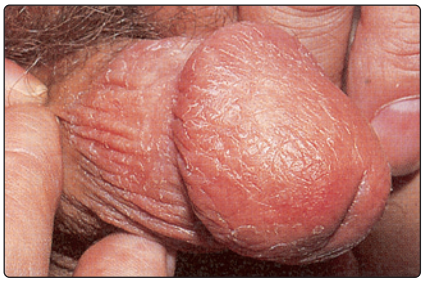


Fig. 64.4 Eczema of the glans penis.

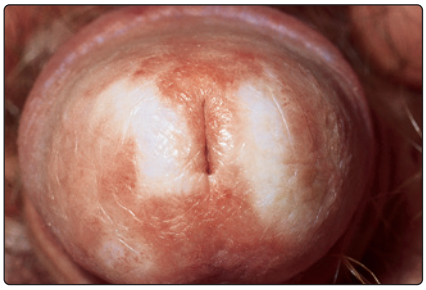


Fig. 64.5 Lichen sclerosus. Changes of low-grade balanitis and perimeatal leukoderma are present on the glans penis. *(From Bunker CB 2004. Male Genital Skin Disease. WB Saunders, Philadelphia.)*

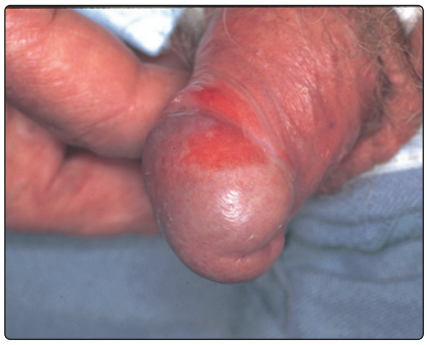


Fig. 64.6 Zoon's balanitis. Moist erythematous involvement of the glans and inner foreskin are seen. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

Genital ulceration

- *Ulceration of the penis* can be due to aphthous ulceration or infection (e.g. herpes simplex). Causes of chronic ulceration are Behçet's disease, forms of vasculitis, pyoderma gangrenosum (p. 93) and bullous disorders (p. 82).
- *Scrotal gangrene* is a necrotizing cellulitis of rapid onset, seen in diabetics. It has a mortality rate of 45%.

Pain syndromes

- *Peno/scroto-dynia* is a condition in which men experience burning or dysaesthesia affecting the genital skin with no demonstrable underlying organic pathology. Most men are middle-aged. Treatment is difficult. There may be psychiatric comorbidity (p. 26).

Perianal skin diseases

Specific presentations include the following:

- *Pruritus ani* is not a diagnosis but the symptom of anal or perianal itching. It is especially seen in middle-class, middle-aged white males. The perianal skin is involved by infective, inflammatory and occasionally neoplastic conditions in 50% of cases. Anal leakage is an aggravating factor, as is difficulty cleaning the area. Faecal contamination of the perianal skin with bacteria, enzymes and allergens causes inflammation and itch. Persistent rubbing induces lichen simplex (p. 41) or maceration, and secondary infection with bacteria or fungi. A compounding contact dermatitis due to allergy to 'over-the-counter' creams is common. Anal carcinoma, fissure or haemorrhoids, and threadworm infestation in children, should be excluded. Treatment requires attention to personal hygiene (daily baths are helpful but avoid the use of soap) and the topical application of an emollient, antiseptic or steroid preparation.
- *Anal fissures* are a type of ulcer. They can be related to pressure from defaecation of hard stools. Perianal fistula is a communication between the anal canal and the skin. It may indicate Crohn's disease.
- *Trauma to the anus* may result from sexual activity. In a child, sexual abuse must be considered.

Genital dermatoses

Female genital dermatoses

- Lichen sclerosus predisposes to squamous cell carcinoma and requires long-term follow-up.
- Vulval intraepithelial neoplasia requires long-term follow-up and cervical screening.
- Chronic ulceration may indicate a blistering disorder or Behçet's syndrome.
- Vulval pain syndromes need a combined approach to management.

Male genital dermatoses

- Lichen sclerosus can result in meatal narrowing. Treat with clobetasol propionate.
- Zoon's balanitis is indolent. It presents as glistening red patches in the uncircumcised.
- Penile intraepithelial neoplasia presents as brownish plaques. Needs follow-up.
- Penile carcinoma presents as an irregular often ulcerating nodule. Biopsy is mandatory if malignancy is suspected.

Pruritus ani

- Is common in middle-class, middle-aged white males.
- May be due to the irritant effects of faecal contamination on perianal skin.
- Anal carcinoma, anal fissure and haemorrhoids must be excluded.
- Local hygiene measures and a topical antiseptic or steroid are prescribed.

- *Balanitis* describes inflammation of the penile skin, e.g. by eczema (Fig. 64.4). *Circinate balanitis* is an eroded or crusted penile eruption seen in Reiter's syndrome (p. 44, Fig. e64.3).
- *Lichen sclerosus* has a predilection for the penis (p. 42). White plaques are seen sometimes with haemorrhagic areas, erosion and sclerosis. The glans, especially around the urethral meatus, is often involved (Fig. 64.5). The severe end result can be balanitis xerotica obliterans (where the meatal aperture is considerably narrowed) or phimosis (Fig. e64.4). Treatment is with a highly potent topical steroid (clobetasol propionate). Chronic lichen sclerosus can predispose to squamous carcinoma (in up to 10% of cases).
- *Lichen planus* of the penis may present with typical purplish papules (p. 42) but sometimes manifests as an erosive form (Fig. e64.5).
- *Penile intraepithelial neoplasia (PIN)*. The terms 'erythroplasia of Queyrat', 'Bowen's disease' and 'bowenoid papulosis' are all variants of PIN (i.e. carcinoma in situ of the penis). PIN presents as patches of warty or scaly plaque on the penile shaft or foreskin, or more moist red patches on the mucosal glans (Fig. e64.6). It is associated with human papilloma virus (especially HPV 16) and HIV infection. Treatment is as for VIN.

Dermatoses such as psoriasis, eczema, lichen planus, lichen sclerosus and vitiligo can involve the perianal skin, giving appearances that may or may not be typical.

- *Haemorrhoids* (piles) are dilatations in the venous system draining the anal region. Bleeding or pain result. Sigmoidoscopy is needed.
- *Anal intraepithelial carcinoma* presents with the appearance of Bowen's disease. Human papilloma virus infection and HIV infection are predisposing factors. The premalignant condition can progress to squamous cell carcinoma.

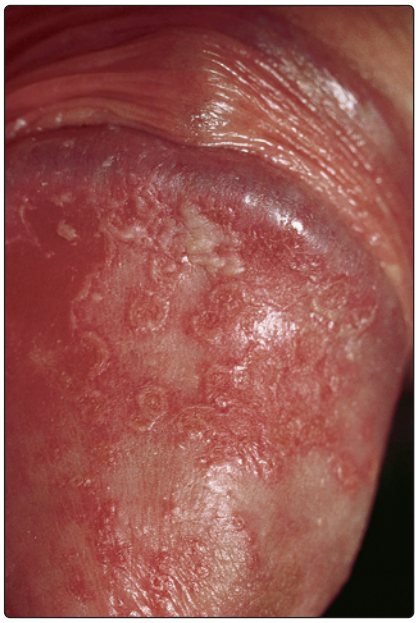
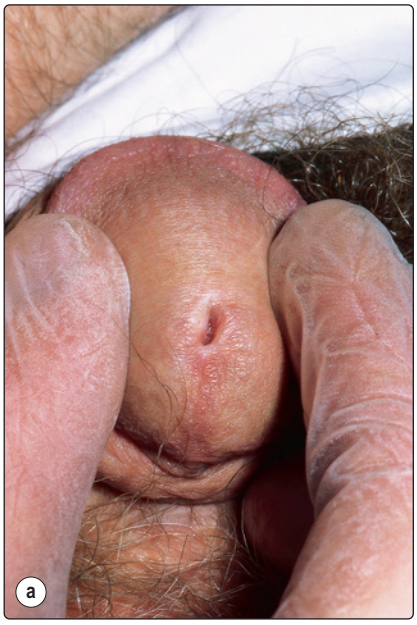


Fig. e64.3 Circinate balanitis of the type seen in Reiter's syndrome. *(From Bunker CB 2004 Male Genital Skin Disease. Saunders, with permission.)*



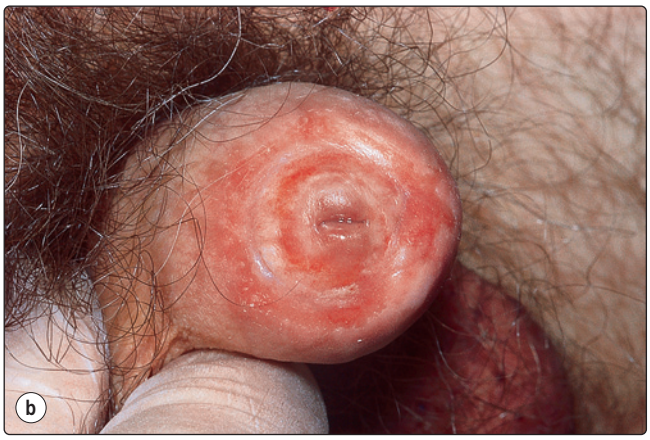


Fig. e64.4 Lichen sclerosus. (a) Lichen sclerosus showing meatal narrowing and perimeatal sclerosis. (b) Lichen sclerosus showing phimosis. *(From Bunker CB 2004 Male Genital Skin Disease. Saunders, with permission.)*

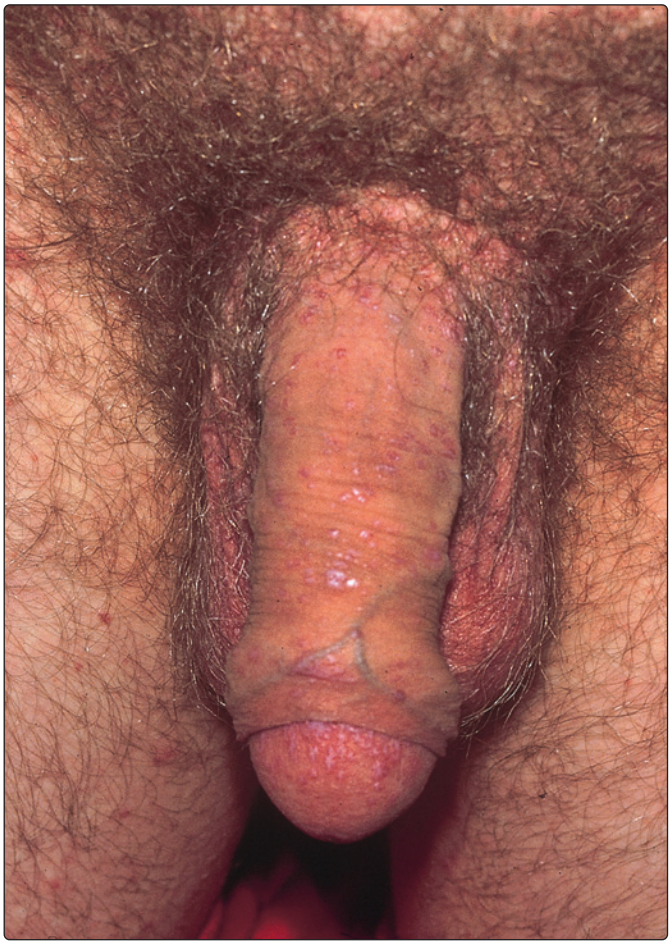


Fig. e64.5 Lichen planus of the penis. Flat-topped papules may become confluent. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

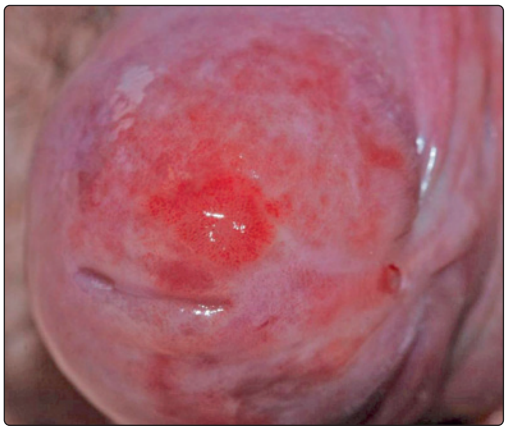


Fig. e64.6 Penile intraepithelial neoplasia. Erythematous changes are present on the glans penis. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Further reading – online sources

More information on genital dermatoses can be obtained through the website of the British Association for Sexual Health and HIV (access via www.bashh.org/) and the International Society for the Study of Vulval Diseases (search under 'For providers'/ resources: access via http://issvd.org).

Further reading – textbooks

Edwards, L., Lynch P.J., 2011. Genital Dermatology Atlas, second ed. Lippincott Williams & Wilkins, Philadelphia, PA.
Bunker, C.B., 2004. Male Genital Skin Disease. WB Saunders, Philadelphia, PA.

65 Racially pigmented skin

Common dermatoses may show variable manifestations in different races due to differences in pigmentation, hair or the response of skin to external stimuli. In addition, some conditions have a distinct racial predisposition. The response of darkly pigmented skin to injury and to certain therapeutic modalities needs to be taken into account when planning a programme of management.

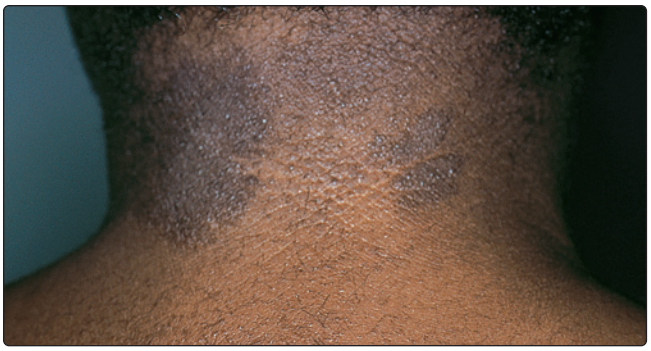


Fig. 65.1 Lichen simplex chronicus showing hyperpigmentation and lichenification.

Definition of race

The characteristics of our species, *Homo sapiens*, are continuously variable, and hence the division into 'races' is – to some extent – artificial. However, there are obvious differences between groups of humans, and these differences have an influence on the appearance of and susceptibility to disease. Most definitions of a '*race*' are unsatisfactory, but perhaps the best is 'a population that differs significantly from other populations in regard to the frequency of one or more of the genes that it possesses'. Obviously, this definition allows even rather small groups to be classified as a race.

It is generally assumed that changes in gene frequency result from mutation, natural selection and 'accidental' loss. Some changes are thought to be the result of adaptation to environmental conditions, although it is not always obvious what advantage is conferred. Racial classification has relied on physical characteristics, often skeletal, although hair form and skin colour are taken into account. The main divisions are the following:

- *Australoid*, e.g. Australian aborigines.
- *Black African*: includes *congoid* and *capoid*, e.g. San (Bushmen) and Khoikhoi (Hottentots).
- *Caucasoid*, e.g. Europeans, peoples of the Mediterranean, Middle East and most of the Indian subcontinent.
- *Mongoloid*, e.g. peoples of East Asia, Eskimos, American Indians.

Racial differences in normal skin

The most obvious difference is in pigmentation, but hair forms and colour also vary. Mongoloid hair is straight and has the largest diameter; black African hair is short, spiralled, drier and more brittle than that of other races; and Caucasoid hair may be wavy, straight or helical. Hair colour is predominantly black in Mongoloids and Africans, and black, blonde or red in Caucasoids. Body hair is most profuse in Caucasoids. The black African stratum corneum differs from that of the Caucasoid by showing greater intercellular adhesion and a higher lipid content.

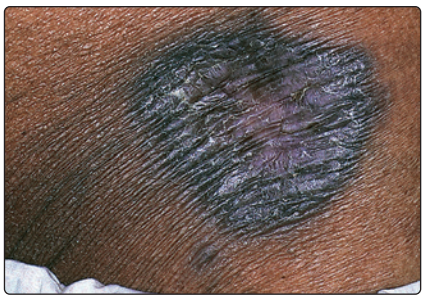


Fig. 65.2 Lichen planus with hyperpigmentation.

Table 65.1 **Causes of hypopigmentation in pigmented skin**

Division	Disorder
Infections	Leprosy, onchocerciasis, pinta, pityriasis versicolor
Papulosquamous disorders	Pityriasis rosea, pityriasis alba, psoriasis (occasionally), seborrhoeic dermatitis
Physical and chemical agents	Burns, cryotherapy, hydroquinone, topical potent steroids
Post-inflammatory	Discoid lupus erythematosus, systemic sclerosis, sarcoidosis
Other	Albinism, vitiligo

Diseases that show racially dependent variations

In pigmented skin, eruptions that appear red or brown in white Caucasoid skin may be black, grey or purple, and pigmentation can mask an erythematous reaction. Inflammation in pigmented skin, e.g. an eczematous process, often provokes a hyperpigmentary (Figs 65.1, 65.2) or sometimes a hypopigmentary (Table 65.1) reaction. Follicular, papular and annular patterns are more common in pigmented skin than in Caucasoid. In addition, some skin disorders show an inter-racial variation in prevalence (Table 65.2).

Table 65.2 **Diseases with racially dependent variations**

Skin disorder	Caucasoid	Mongoloid	Black African
Acne	Most severe	Least common	Hyperpigmented lesions
Atopic eczema	Most common with the Western lifestyle	Lichenification is seen	Follicular and hyperpigmented lesions are found
Keloid	May occur	More frequent	More frequent
Lichen planus	Can show some pigmentation	Often hyperpigmented	Often hyperpigmented
Melanocytic naevi	Very common	A few may be present	Uncommon
Psoriasis	Common (2% prevalence)	Rare (0.3% prevalence but increasing)	East > West Africans: plaques bluish, leave hyper- or hypopigmentation
Sarcoidosis	Less common	Less common	In USA, 10 times more common than in Caucasoids
Skin cancer	Most common in northern Europeans	Intermediate prevalence	Uncommon
Vitiligo	Same prevalence, least obvious	Same prevalence, more obvious	Same prevalence, most obvious

In pigmented skin, eruptions that appear red or brown in white Caucasoid skin may be black, grey or purple, and pigmentation can mask an erythematous reaction. Inflammation in pigmented skin, e.g. an eczematous process, often provokes a hyperpigmentary (Figs 65.1, 65.2 and Fig. 39.2) or sometimes a hypopigmentary (Table 65.1) reaction. Follicular, papular and annular patterns are more common in pigmented skin than in Caucasoid. In addition, some skin disorders show an inter-racial variation in prevalence (Table 65.2).

Diseases with a distinct racial or ethnic predisposition

Hair disorders

Racially dependent hair conditions are most common in black Africans and include the following:

- *Folliculitis (acne) keloidalis* describes discrete follicular papules, often keloids, at the back of the neck in African males (Fig. 65.3). Intralesional steroids may help.
- *Pseudofolliculitis barbae* is a common disorder in black African men and is characterized by inflammatory papules and pustules in the beard area. It is thought to result from hairs growing back into the skin (Fig. 65.4). Treatment is difficult but includes attention to shaving technique and the topical use of antibiotics and steroids.
- *Traction alopecia* is mainly seen in black Africans because of the practice of plaiting or tightly braiding the hair (Fig. 65.5). Hairs are loosened from their follicles. The temples are often affected. Initially the alopecia is reversible but if maintained for years it becomes permanent.
- *Central centrifugal cicatricial alopecia* is a slowly progressive symmetrical scarring alopecia centred on the vertex of the scalp in black African women. It is contributed to by hot combing and the use of caustic haircare products but these cannot fully explain the pathogenesis.

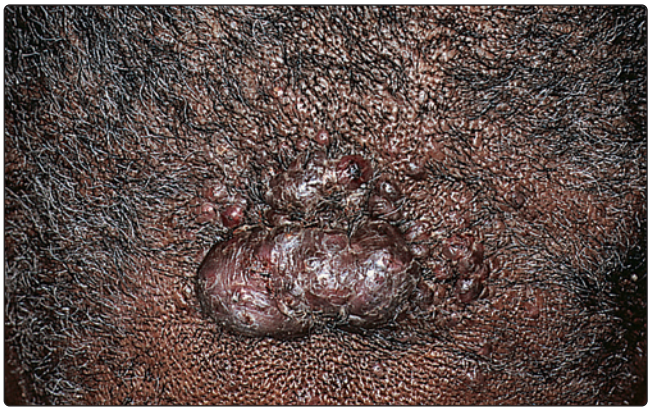


Fig. 65.3 Folliculitis (acne) keloidalis.

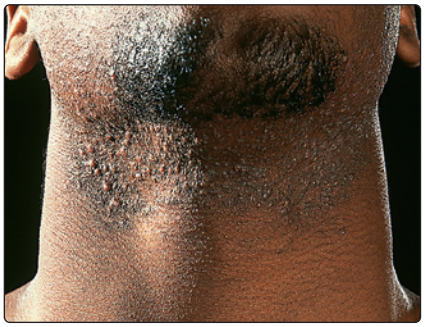


Fig. 65.4 Pseudofolliculitis barbae.

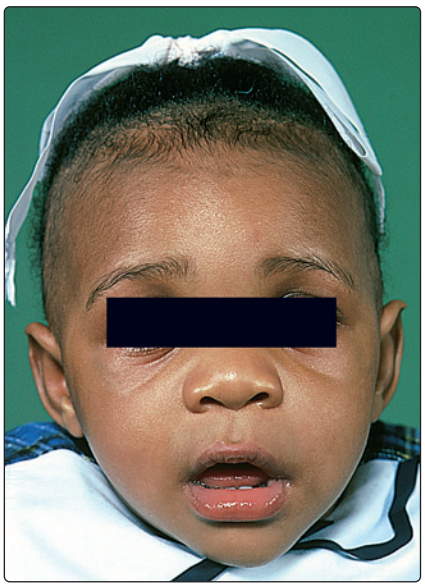


Fig. 65.5 Traction alopecia.

Pigmentary changes

Pigmentary abnormalities, as both a variation of 'normal' and otherwise, are also common. These include the following:

- *Dermatosis papulosa nigra* describes small, seborrhoeic wart-like papules often seen on the face in black Africans.
- *Lines of hypo- or hyperpigmentation*, often on the upper arms, are not infrequently found in black Africans.
- *Longitudinal nail pigmentation* and macular pigmentation of palms and soles occur mainly in black Africans.
- *Mongolian spot* is a slate-brown pigmentation at the sacral area in a baby and is found in 100% of Mongoloids; ≥70% of Africans and 10% of Caucasoids. It usually fades by the age of 6 years.
- *Naevus of Ota* is a macular, slate-grey pigmentation in the upper trigeminal area, which may involve the sclera (Fig. 65.6). It is seen most frequently in Mongoloids.

Other conditions

A racial preponderance is also seen with the following conditions:

- *Sickle cell disease* occurs in black Africans. The main cutaneous findings are painful oedema of the hands and feet, caused by infarction in the small bones, and leg ulceration.
- *Vascular naevi*, such as the port-wine stain naevus, and melanocytic naevi, are more common in Caucasoids.

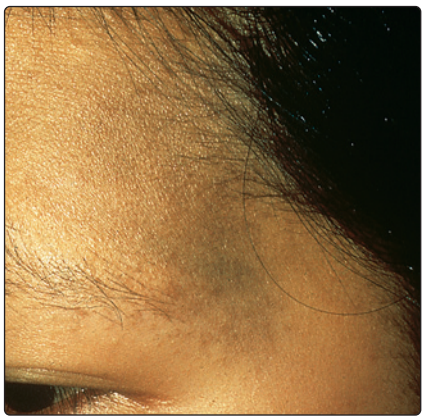


Fig. 65.6 Naevus of Ota.

Racially pigmented skin

- **A race** is a genetically defined group, although the characteristics of *Homo sapiens* are continuously variable.
- **The main racial groups** are Mongoloids, black Africans and Caucasoids (the last include Middle East and Indian subcontinent peoples).
- **Eruptions that are red or brown** in Caucasoid skin may appear *black*, *grey* or *purple* in people with pigmented skin.
- **Lichenification:** inflammatory dermatoses tend to become *lichenified* in Mongoloids and may be *follicular* in black Africans.
- **Hypopigmentation** may follow from skin trauma, e.g. burns or from cryotherapy, topical steroids and some dermatoses, in pigmented skin.
- **Hair disorders**, e.g. pseudofolliculitis, keloidal change or traction alopecia, are common in black Africans.
- **Pigmentary lines** are frequently found on the limbs (e.g. the outer upper arm) or nails in black Africans and other races.
- **Sacral mongolian spots** are found in most Mongoloid and black African babies, but in only a few Caucasoid infants.
- **Vascular and melanocytic naevi** (e.g. port-wine stain) are more common in Caucasoids than in other races.

- *Central centrifugal cicatricial alopecia* is a slowly progressive symmetrical scarring alopecia centred on the vertex of the scalp in black African women. It is contributed to by hot combing and the use of caustic haircare products but these cannot fully explain the pathogenesis (Fig. e65.1).
- *Dissecting cellulitis of the scalp*. This is a chronic inflammatory disease of the scalp most common in black African males. Tender fluctuant swellings develop on the vertex of the scalp with destruction of hair follicles. Permanent scarring results. The treatment consists of long-term antibiotics, oral corticosteroids or oral retinoids.
- *Pityriasis rotunda* is a rare form of acquired ichthyosis that may develop in people of black African descent. It is characterized by large discrete circular patches that are usually located to the trunk. They lack inflammatory change but may show hyperpigmentation (or occasionally hypopigmentation).
- *Other diseases*. Lupus erythematosus and sarcoidosis have a higher prevalence in people of black African origin. Pemphigus vulgaris may be more common in Caucasians from the Indian subcontinent. Rosacea is more frequent in Caucasians with a Celtic complexion.

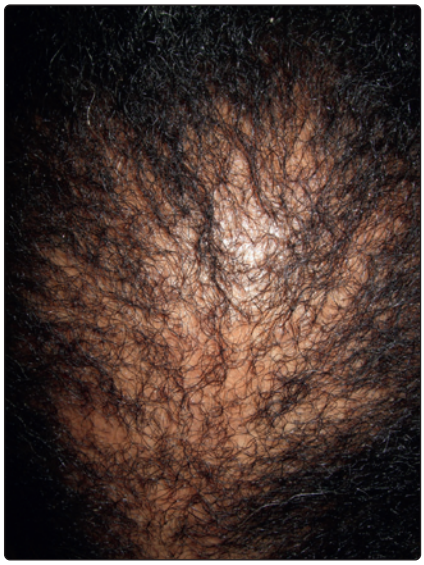


Fig. e65.1 Central centrifugal cicatricial alopecia in an African-American woman. *(From Bolognia JL, Jorizzo JL, Schaffer JV 2012 Dermatology, 3rd Edn. Saunders, with permission.)*

Further reading – online sources

More information on skin disease in people with ethnic skin types (including additional photographs) can be obtained at the Brownskin website (access via http://www.brownskin.net).

Further reading – textbooks

Alexis, A.F., Barbosa, V.H., 2014. Skin of Color: A Practical Guide to Dermatologic Diagnosis and Treatment. Springer, New York.

66 Occupation and the skin

Skin disorders, after stress and musculoskeletal problems, are the commonest reported cause of occupational disease and are responsible for much lost productivity. An occupational dermatosis is defined as a skin condition that is primarily due to components of the work environment and would not have occurred unless the individual were doing that job.

Diagnosis

Proving a work association can be difficult. The following give clues:

- Contact with a known noxious agent.
- Similar skin disease in other workers.
- Consistent exposure-to-onset time course.
- Attacks appear with exposure, improve on withdrawal.
- Site and type of eruption consistent with exposure.
- Corroboration by patch testing.

Contact dermatitis is the most common work-related skin disease and is more often irritant than allergic. Contact urticaria, particularly to latex, is now well-recognized. Other occupational dermatoses are listed in Table 66.1. Certain infections, e.g. anthrax (p. 53), orf (p. 55) and tinea corporis (p. 60) may be occupational. Heat, cold, ultraviolet radiation, vibration and X-rays can cause industrial disease.

Table 66.1 **Rarer occupational skin disorders**

Condition	Presentation	Occupational exposure
Argyria (Fig. 66.1)	Slate-grey pigmentation on face, hands, sclerae	Industrial processes, e.g. silver smelters
Chloracne (Fig. 66.2)	Multiple open and closed comedones on cheeks and behind ears	Halogenated aromatic hydrocarbons, e.g. contamination during manufacture
Occupational vitiligo (p. 78)	Symmetrical pigment loss on face and hands	Substituted phenols or catechols in oils, at coking plant
Tar keratoses (Fig. 66.3)	Small keratotic warts on face and hand, premalignant	Tar and pitch, e.g. road work or coking plant; UV is a co-carcinogen
Vibration white finger (p. 74)	Blanching and pain in digits, later swelling and impaired fine movement	Hand-held vibrating tools, as used by rock drillers or chainsaw operators

Table 66.2 **Contact dermatitis hazards in selected occupations**

Occupation	Irritants	Allergens
Bakers	Flour, detergent, sugar, enzymes	Flavouring, oil, antioxidant
Building-trade workers	Cement, glass wool, acid, preservatives	Cement (Cr, Co), rubber, resin, wood
Caterers, cooks	Meat, fish, fruit, vegetables, detergent, water	Vegetables, fruit, cutlery (Ni), rubber gloves, spice
Cleaners	Detergent, solvent, water, friction	Rubber gloves, nickel, fragrance
Dental personnel	Detergent, soap, acrylate, flux	Rubber, acrylate, fragrance, mercury
Electronics assemblers	Solder, solvent, fibreglass, acid	Cr, Co, Ni, acrylate, epoxy resin
Hairdressers	Shampoo, bleach, perm lotion, soap, water, friction	Para-phenylenediamine dye, rubber, fragrance, thioglycolate
Metal workers	Cutting fluid, cleanser, solvent	Preservative, Ni, Cr, Co, antioxidant
Office workers	Paper, fibreglass, dry atmosphere	Rubber, Ni, dye, glue, copying paper
Textile workers	Solvent, bleach, fibre, formaldehyde	Formaldehyde resin, dye, Ni
Veterinarians, farmers	Disinfectant, animal secretion	Rubber, antibiotics, plants, preservative

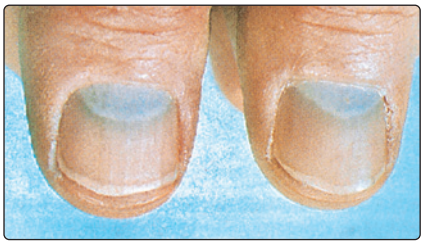


Fig. 66.1 Blue discoloration of the nails due to argyria in a silver smelter.

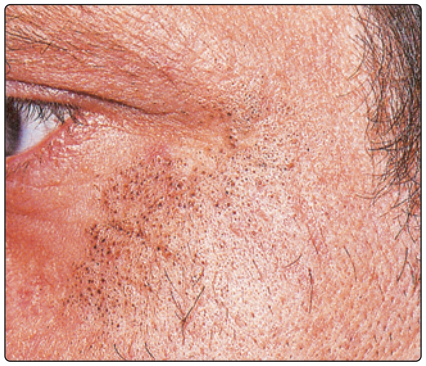


Fig. 66.2 Chloracne showing comedones in a man exposed to dioxin contaminants.

Contact dermatitis

It is often difficult to differentiate between allergic and irritant causes.

Aetiopathogenesis

Many industrial substances are irritants and some are also allergens (p. 37). Water, detergents, alkalis, coolant oils and solvents are important irritants. Common allergens include: chromate, rubber chemicals, preservatives, nickel, fragrances, epoxy resins and phenol-formaldehyde resins (Table 66.2).

Irritant dermatitis frequently results from cumulative exposure to multiple types of irritant. An irritant dermatitis increases epidermal penetration by allergens and, because of this, it predisposes to superimposed contact sensitization. Similarly, allergic contact dermatitis renders skin vulnerable to attack by irritants.

Constitutional factors, especially atopic eczema, predispose to contact dermatitis. Environmental factors such as physical friction, occlusion, heat, cold, dry air from air-conditioning or sudden swings in air temperature or humidity also have an effect.

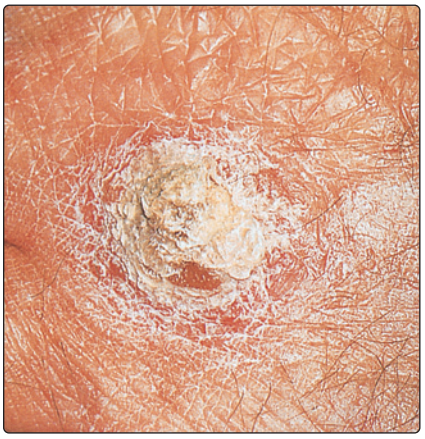


Fig. 66.3 A tar keratosis in a coking plant worker.

Clinical presentation

The hands are affected, alone or with other sites, in 80–90% of occupational cases. The arms can be involved if not covered, and the face and neck are affected if there is exposure to dust or fumes. Cement workers often have lower leg and foot dermatitis in addition to hand changes. Allergy to rubber chemicals can cause dermatitis from rubber gloves or boots. Some workers develop 'hardening', an adaptive tolerance to irritants or allergies.

Occupational dermatitis appears at any age, but peaks at each end of working life.

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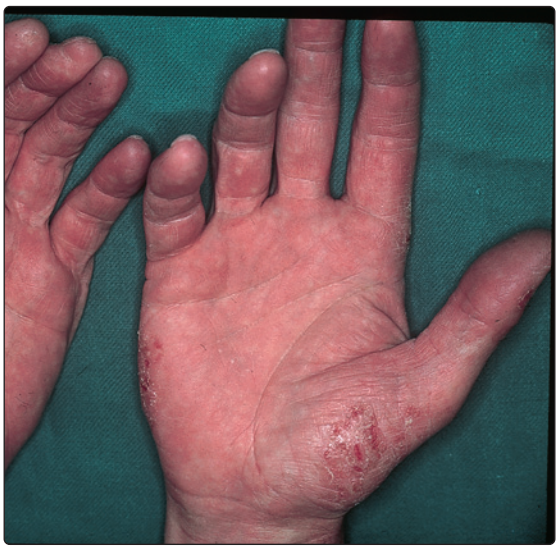

Fig. e66.1 Hand dermatitis in a man who wore rubber gloves in his work as a dental technician. Patch testing showed contact allergy to chemicals used in rubber manufacture. *(From Gawkrodger DJ 2004 Rapid Reference Dermatology, Mosby, with permission.)*

Case history 1

Hand dermatitis

A 17-year-old girl who had had childhood atopic eczema started as a hairdressing apprentice. Within 8 weeks, she developed hand dermatitis (Fig. 66.4) unresponsive to emollients and topical steroids. Patch testing was positive for ammonium thioglycolate (a permanent wave agent) and nickel. A diagnosis was made of contact dermatitis with irritant and allergic components, in an individual with underlying endogenous eczema. Her dermatitis cleared within weeks when she left hairdressing to work in an office.

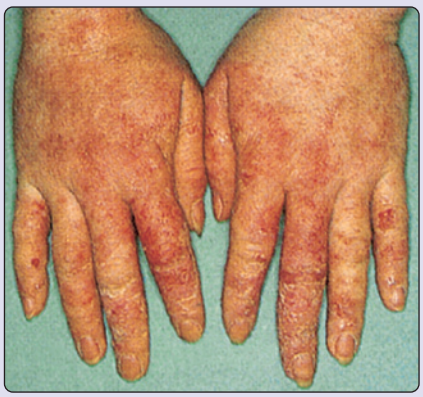

Fig. 66.4 Hand dermatitis in a hairdresser.

Case history 2

Chromate dermatitis

A 30-year-old man had been employed for 3 years making pipes out of cement. This involved exposure to wet cement. Despite wearing gloves and overalls, he developed dermatitis on the hands (Fig. 66.5), arms and lower legs. Patch testing showed chromate allergy. He received compensation for having an industrial disease but, even when he changed his occupation to driving, he continued to have hand dermatitis.

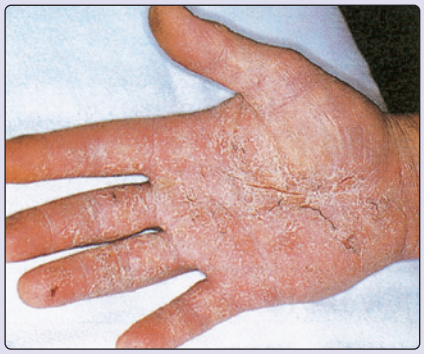

Fig. 66.5 Hand dermatitis in a cement worker.

Case history 3

Contact urticaria

A 40-year-old female nurse gave a 12-month history of itching, swelling and redness on her hands (Fig. 66.6), which developed within minutes of wearing disposable latex gloves. Patch testing was negative, but a prick test was positive for latex (confirmed by specific IgE test). Her symptoms resolved when she changed to nitrile gloves. Provision of latex-free nitrile disposable gloves to healthcare workers seems to have reduced the prevalence of latex allergy.

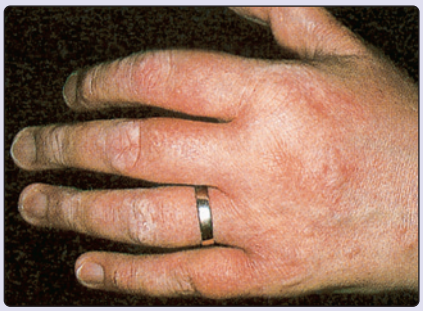

Fig. 66.6 Contact urticaria to latex.

In bakers and hairdressers, dermatitis appears early. In cement workers, chromate dermatitis requires a few years to develop. Cumulative irritant dermatitis appears after several years' exposure.

Differential diagnosis

Contact dermatitis due to non-occupational exposure and endogenous eczemas need considering. Often, occupational dermatitis is multifactorial, with irritants, allergens, endogenous factors and secondary bacterial infection all causally involved.

Management

Patch testing (p. 37) is required if there is exposure to known allergens. A factory visit helps to ascertain the exact nature of irritant or allergen exposure.

Once recognized, occupational exposure to a causative agent can be minimized, but this does not always produce an improvement. Chromate allergy is particularly intransigent. Any dermatitis is treated along standard lines with special attention to hand care. Barrier creams are of dubious value.

Contact urticaria

Some proteins and chemicals provoke immediate urticaria (p. 80). The release of mast cell histamine or other mediators may or may not be immunoglobulin (Ig)E mediated. Pruritus, erythema and whealing appear within minutes and last a few hours.

Occupational contacts include latex in rubber gloves, foods (e.g. fish, potato, eggs, flour, spices, meats and numerous fruits), *Myroxylon pereirae* (a perfume and flavouring agent) and animal saliva. Contact dermatitis may coexist.

Latex contact urticaria has been a problem in healthcare workers and other occupations. Anaphylaxis may occur if there is a massive latex exposure, e.g. in a patient exposed to latex from a surgeon's gloves during abdominal surgery.

Prevention

Reducing the contact time between the skin and noxious substances is the aim. It is achieved by:

- improved work practices, e.g. increased automation
- substituting an alternative, e.g. nitrile gloves instead of latex rubber
- provision of protective clothing
- taking better care of the skin.

Recognizing an occupational disease may highlight faulty work practices that can be corrected. Compensation may be due.

Occupation and the skin

- **Occurrence:** industrial skin disease is common, especially contact dermatitis.
- **Causation:** occupational contact dermatitis is caused more by irritants than by allergens but is often multifactorial, with endogenous factors frequently being involved in addition.
- **Predisposition:** previous atopic eczema predisposes to occupational contact dermatitis.
- **Patch testing:** can help identify an allergen, e.g. chromate or rubber chemicals.
- **Contact urticaria** to latex has been a risk in healthcare workers and other occupations, but appears less so today.
- **Prevention:** occupational skin disease is minimized by reducing the contact time of noxious agents with the skin and by increasing awareness of the problem.

Chloracne

Chloracne represents systemic toxic exposure to a chemical. Typical skin signs include sheets of comedones especially in the malar and retroauricular areas, sometimes with cysts and inflammatory papules (Fig. 66.2). These take some weeks to develop except where there has been massive exposure. Chloracnegens are typically polyhalogenated aromatic hydrocarbons, such as dioxins or chlorophenols (the latter are used in herbicides). Some chloracnegens are highly potent and toxic at very small doses. Exposure is usually through the skin but can be by the oral or inhalation route. Systemically, the liver and nervous system can be affected.

Treatment is difficult and usually consists of waiting for months or years until the offending chemical clears from the body. Some mineral oils can induce an acneiform eruption where they have contact with the skin, e.g. on the thighs (soaking through overalls), but this is an oil folliculitis and not chloracne.

Occupational vitiligo (leukoderma)

Some chemicals, e.g. the substituted phenols (such as para-tertiary-butylphenol and para-tertiary-butylcatechol), are toxic to melanocytes. Their absorption through the skin can induce depigmentary changes that may be indistinguishable from common vitiligo (p. 78). Making the diagnosis requires the demonstration of exposure of the individual to a known depigmenting agent. Diagnosing an outbreak is easier if several people are affected at a place of work. The treatment is to remove exposure to the offending chemical but often this does not result in repigmentation.

Occupational skin cancers

Squamous cell carcinoma of the scrotum in chimney sweeps exposed to coal tar products was one of the first occupational diseases to be described (in 1775, by Percival Pott). Skin cancers related to tar exposure (polycyclic hydrocarbons are the carcinogens) were still quite common in Britain in the mid-20th century. Fig. 66.3 shows a tar keratosis, which is a premalignant change.

Vibration white finger (hand–arm vibration syndrome)

Chronic exposure to vibrating power tools, e.g. in coal miners or forestry and construction workers, can damage endothelial vasoregulatory mechanisms. A Raynaud's type vasoconstriction in the fingers results, often also with neurological changes.

Further reading – online sources

The Health and Safety Executive website has extensive information on occupational skin problems (access via http://www.hse.gov.uk/), as does the Institute of Occupational Safety and Health (access via http://www.iosh.co.uk/) and the Centers for Disease Control and Prevention (access via http://www.cdc.gov).

Further reading – textbooks

English, J.S.C. (Ed.), 1999. A Colour Handbook of Occupational Dermatology. Manson, London.

Rustemeyer, T., Elsner, P., John, S.M., Maibach, H.I. (Eds.), 2012. Kanerva's Occupational Dermatology, second ed. Springer, Berlin.

67 Immunological tests

Clinical and laboratory tests of an immunological nature are valuable in the diagnosis and management of certain skin diseases. Patch tests are helpful in the investigation of *contact dermatitis*, serum immunoglobulin (Ig)E tests or prick tests are sometimes of use in *atopic disease*, and immunofluorescent studies on biopsied skin (or with serum) are essential in the diagnosis of *bullous disorders* and in some other conditions such as connective tissue diseases (e.g. lupus erythematosus) or vasculitis.

Skin-prick tests

Skin-prick testing detects *immediate* (*type I*) *hypersensitivity*. The reaction is mediated by the antigen-triggered IgE-mediated release of vasoactive substances from skin mast cells (p. 11). Small drops of commercially prepared antigen solutions are placed on marked areas on the forearm and lightly pricked into the skin using separate blunt lancets. The stratum corneum of the epidermis is punctured by gently pressing the blunt lancet perpendicular to the skin surface through the test solution. It is important to develop a prick testing technique that is reproducible. Food allergens are often tested by pricking the fresh food and then the skin (prick to prick testing). The sites are inspected at 15 min, and a positive result is regarded, by convention, as one showing a wheal of ≥3 mm (Fig. 67.1). Patients should have stopped antihistamines 48 h before the test. Prick tests are used to demonstrate allergy to aeroallergens (e.g. house-dust mite) or to foods (e.g. hen's egg or peanut), and contact urticaria to latex (p. 133). A positive test correlates well with a positive allergen-specific IgE test (usually an enzyme-linked immunosorbent assay [ELISA]; the radioallergosorbent test [RAST] is no longer used). The risk of anaphylaxis caused by skin testing is very small, but resuscitation facilities, including adrenaline (epinephrine) for intramuscular injection, antihistamines and oxygen are recommended, especially for testing of food allergy in high-risk subjects (asthmatics).

Patch testing

The epicutaneous patch test detects *cell-mediated* (*type IV*) *hypersensitivity* (p. 11). It is very helpful in the investigation of contact dermatitis. Commercially prepared allergens are available in the correct concentration for testing, usually in petrolatum (or sometimes water) as a diluent. (See Fig. 18.5 for details of the procedure.)

Immunofluorescence

Immunofluorescence, either direct (on the patient's skin) or indirect (using the patient's serum reacted with an animal substrate) (Fig. 67.2), is helpful in making a diagnosis in the *autoimmune blistering diseases* (Table 67.1). Bullous disorders such as pemphigoid (Fig. 67.3) and pemphigus (Fig. 67.4 and p. 82) are characterized by the deposition of organ-specific autoantibodies (usually IgG) in the skin and, less easily demonstrated, by the presence of these autoantibodies in the serum. Dermatitis herpetiformis (Fig. 67.5) and other conditions such as leukocytoclastic vasculitis or lupus erythematosus often show the deposition of immunoglobulin or complement components in the patient's skin (but negative indirect immunofluorescence).

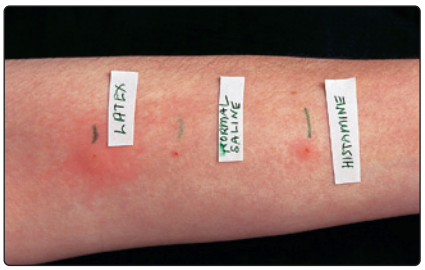

Fig. 67.1 A positive prick test to latex is seen in a latex-allergic subject. The wheal to histamine is shown as a positive control.

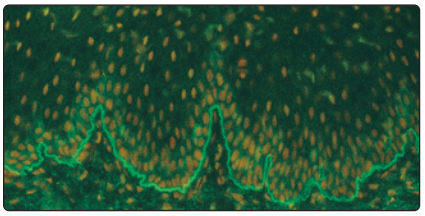

Fig. 67.3 Bullous pemphigoid. Indirect immunofluorescence demonstrates a linear band of IgG antibodies along the basement membrane zone (BMZ) using monkey oesophagus as substrate. These antibodies are directed against bullous pemphigoid antigens (MW 230 and 180 kDa), proteins located within the adhesion complex of the hemidesmosomes and synthesized by basal keratinocytes.

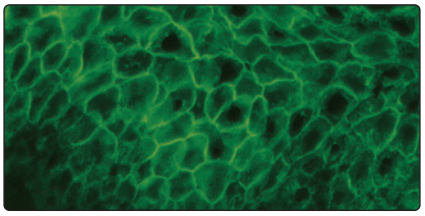

Fig. 67.4 Pemphigus vulgaris. Direct immunofluorescence demonstrates IgG antibodies, directed against desmoglein 3 (MW 130 kDa), a desmosomal cadherin involved in mediating epidermal intercellular adhesion, showing up in a chicken-wire pattern throughout the epidermis.

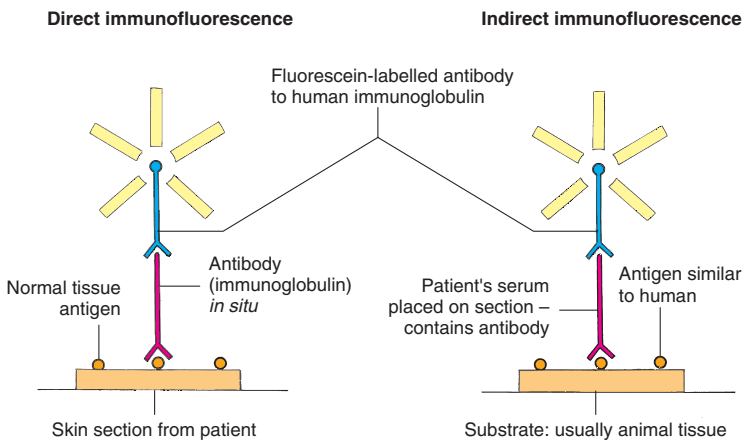

Fig. 67.2 Immunofluorescence. In *direct immunofluorescence*, usually done on perilesional skin, the antibodies or complement components are detected by reacting the freshly cut skin sections with an antibody directed against the specific immunoglobulin or complement fraction and labelled with a fluorescent marker, which is visualized with a fluorescence microscope. The *indirect method* is a two-step procedure that involves the use of cut sections of an animal substrate (e.g. monkey oesophagus) or human skin. The patient's diluted serum (containing the putative antibody) is placed on this section, incubated for an hour or so and then revealed using a fluorescein-tagged antihuman immunoglobulin antibody that is demonstrated by examining with ultraviolet radiation. Human skin, split at the dermoepidermal junction by saline incubation, may be used as a substrate to distinguish variants of pemphigoid, when deposition of the antibody on the epidermal or dermal side of the split can be diagnostic.

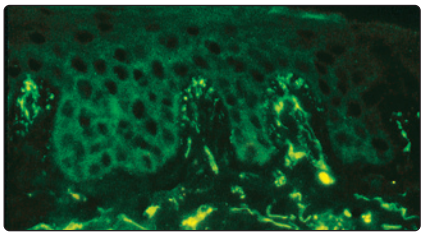

Fig. 67.5 Dermatitis herpetiformis. Direct immunofluorescence reveals the deposition of IgA in a granular pattern at the dermal papillae. This is diagnostic for dermatitis herpetiformis (p. 4), although it is unlikely that the eruption is solely due to the presence of this IgA.

Table 67.1 **Immunofluorescence in bullous disease**

Bullous disorder	Direct immunofluorescence (skin)	Indirect immunofluorescence (serum)
Bullous pemphigoid	Linear IgG/C3 at BMZ in 80%	Linear IgG at BMZ in 75% (IgA/IgM in 25%)
Pemphigus vulgaris	Intercellular epidermal IgG/C3 in 100% (IgA/IgM in 20%)	Intercellular IgG in 80% (the antibody titre reflects disease activity)
Dermatitis herpetiformis	Granular IgA deposition at dermal papilla (100%)	Absent
Linear IgA disease	Linear IgA at BMZ in 80% (IgG/IgM/C3 in 10%)	Linear IgA at BMZ found in some cases

BMZ, basement membrane zone.

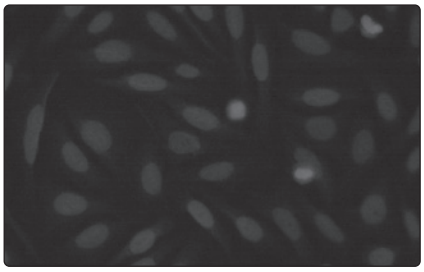

Fig. 67.6 Positive antinuclear immunofluorescence by cell-line staining (HEP2000). The antibodies may be targeting a variety of nuclear antigens. Typically this is then explored by recombinant antigen testing. However, most laboratories now miss the cellular step and proceed direct to testing panels of recombinant nuclear antigens with ELISA. Homogenous nuclear staining is shown, which is typically seen in systemic lupus erythematosus (associated with anti-dsDNA, anti-nucleosomal and antihistone antibodies). The nucleolar staining may be seen in scleroderma, possibly suggesting an overlap syndrome in this case.

Table 67.2 **ANA – extractable nuclear antigen panel**

		Sensitivity (%)	Specificity (%)
Anti-Sm antibody	SLE	75	95
Anti-Ro (SS-A) antibody	Sjogren's syndrome SLE	90 40	50 50
Anti-La (SS-B) antibody	Sjogren's syndrome SLE	80 30	60 50
Anti-Jo-1 (histidyl tRNA synthetase) antibody	Polymyositis, dermatomyositis	40	95
Anti-Scl-70 (topoisomerase-1) antibody	Scleroderma SLE	35 2.50	90 10
Anti-ribonucleoprotein (RNP) antibodies	Mixed CTD SLE	90 35	65 60

(From: Phan TG, Wong RC, Adelstein S. 2002. Autoantibodies to extractable nuclear antigens: making detection and interpretation more meaningful. Clin Diagn Lab Immunol 9:1–7.)

Direct immunofluorescence assays of patient serum for antinuclear antigens and other connective tissue disease antigens were routinely undertaken on cell lines, but have largely been superseded by gel electrophoresis of panels of recombinant proteins, with the microscopic examination of cellular binding of patient antibodies (e.g. using HEP2 cells) restricted for difficult cases (Fig. 67.6). Typical panels of recombinant proteins are listed in Table 67.2.

Newer approaches to indirect immunofluorescence include ELISA assays using plate bound skin antigen to identify circulating skin-specific IgG. These provide increased sensitivity and immediate identification of the target antigen. However, while the list of available recombinant antigens is limited, this process cannot replace the standard methodology described above.

Tests for T cell specificity

Most immunological assays in routine practice identify antibody specificity. However, assays to determine the specificity of T cells in *cell-mediated* (*type IV*) *hypersensitivity* immune responses are available in some specialist centres and this is likely to become more widespread. Such assays are particularly valuable in situations where patch testing is not appropriate or not sensitive. This arises in the context of T cell mediated drug allergic reactions where the culprit drug is unknown. Measurements of drug induced lymphocyte proliferation (LPA; syn. LTT) has been used in research laboratories for many years, but relies on measures of radioactivity with incorporation or 3H-TdR. More recently, the use of ELISpot detection of drug induced cytokine release has been utilised to identify culprit drugs following drug hypersensitivity reactions such as DRESS and TEN (see Ch. 45).

Immunological tests

- **Prick tests** reveal type I (IgE-mediated) hypersensitivity and can demonstrate air-borne (e.g. house-dust mite), food and latex allergies.
- **Patch tests** detect type IV (cell-mediated) hypersensitivity and are helpful in investigating contact dermatitis, e.g. in hand eczema.
- **Direct immunofluorescence** demonstrates immunoglobulin and complement deposition in the skin and is very useful in the diagnosis of bullous disorders, e.g. pemphigoid or pemphigus.
- **Indirect immunofluorescence** uses an animal substrate to detect antibodies in a patient's serum. It is often positive in pemphigus and pemphigoid, and sometimes in linear IgA disease, but is negative in dermatitis herpetiformis.
- **Autoantibodies in bullous pemphigoid (BP)** are against BP antigens of molecular weight (MW) 230 and 180 kDa and, in pemphigus vulgaris, against desmoglein 3 antigen (MW 130 kDa). The autoantigen, if any, in dermatitis herpetiformis is not currently known.
- **Autoantibodies in connective tissue diseases** are useful in the diagnosis of various clinical entities, but with varying sensitivity and specificity.

Direct immunofluorescence assays of patient serum for antinuclear antigens and other connective tissue disease antigens were routinely undertaken on cell lines, but have largely been superseded by gel electrophoresis of panels of recombinant proteins, with the microscopic examination of cellular binding of patient antibodies (e.g. using HEP2 cells) restricted for difficult cases (Fig. 67.6 and Fig. e67.1). Typical panels of recombinant proteins are listed in Table 67.2.

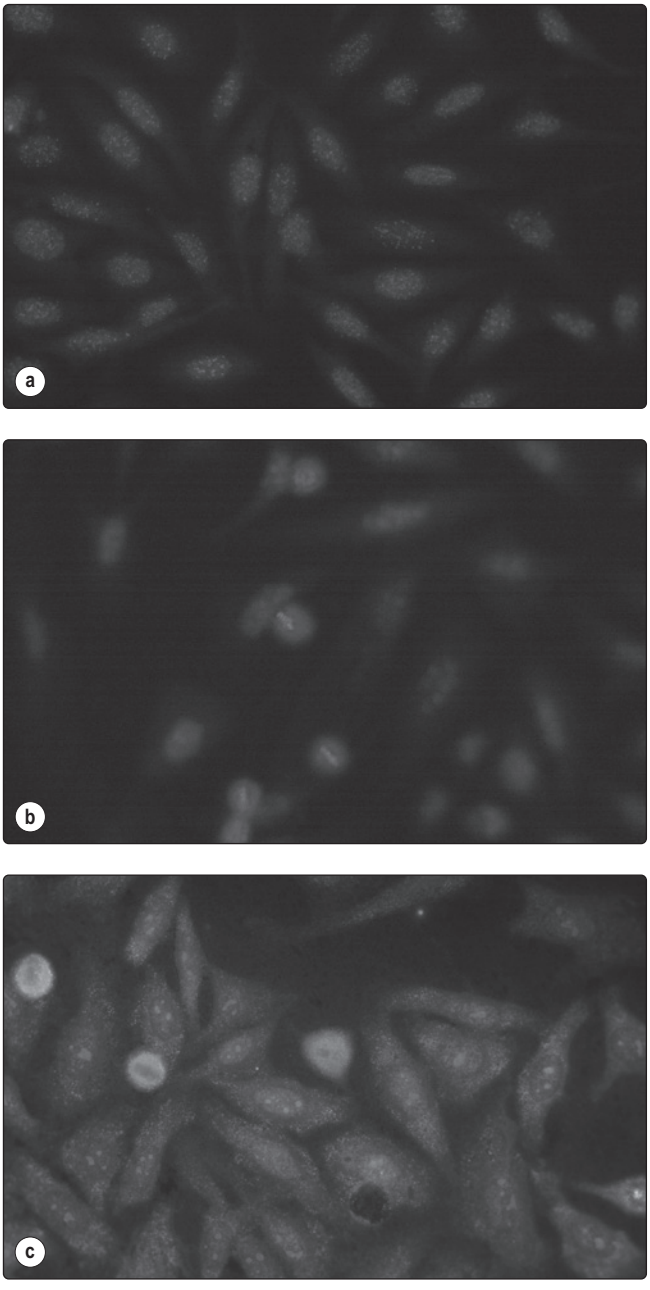

Fig. e67.1 Positive antinuclear immunofluorescence. (a) Anti-centromere positive antinuclear immunofluorescence showing the nuclear speckled pattern typical of limited cutaneous form of systemic sclerosis (previously known as CREST syndrome). (b) Anti-centromere positive antinuclear immunofluorescence showing the laddering at metaphase. (c) Anti-Jo-1 positive antinuclear immunofluorescence with speckled cytoplasmic staining and also some nucleolar fluorescence, as seen in approximately 35% of patients with dermatomyositis and defining the cohort at high risk of lung fibrosis.

Most immunological assays in routine practice identify antibody specificity. However, assays to determine the specificity of T cells in *cell-mediated* (*type IV*) *hypersensitivity* immune responses are available in some specialist centres and this is likely to become more widespread. Such assays are particularly valuable in situations where patch testing is not appropriate or not sensitive. This arises in the context of T cell mediated drug allergic reactions where the culprit drug is unknown. Measurements of drug induced lymphocyte proliferation (LPA; syn. LTT) has been used in research laboratories for many years, but relies on measures of radioactivity with incorporation or 3H-TdR. More recently, the use of ELISpot detection of drug induced cytokine release has been utilised to identify culprit drugs following drug hypersensitivity reactions such as DRESS and TEN (see Ch. 45) (Fig. e67.2).

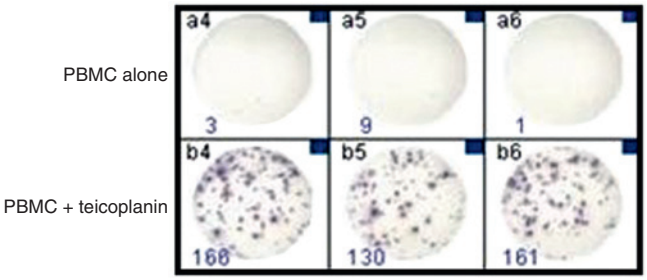

Fig. e67.2 ELISpot assay demonstrating IFN-γ secretion by PBMC in response to teicoplanin in an individual who had suffered DRESS syndrome (p. 90).

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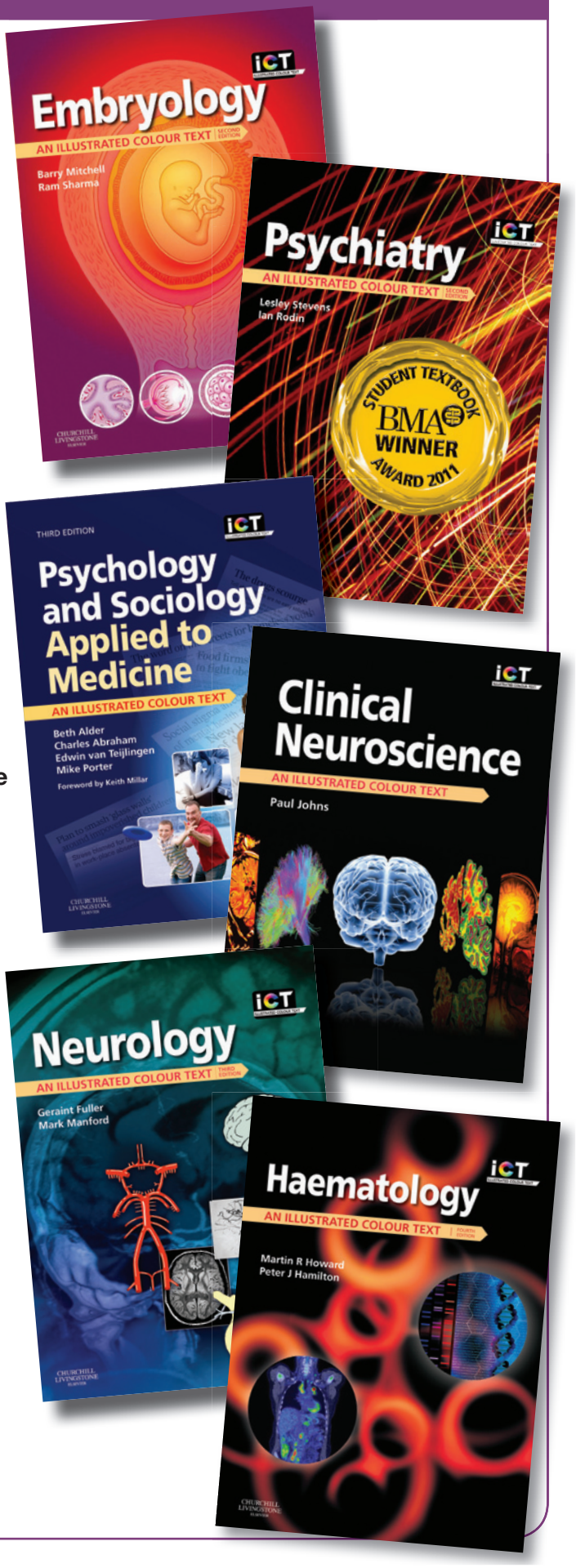

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